PCT/EP2005/001362

10.02.05

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PRIORITY DOCUMENT

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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

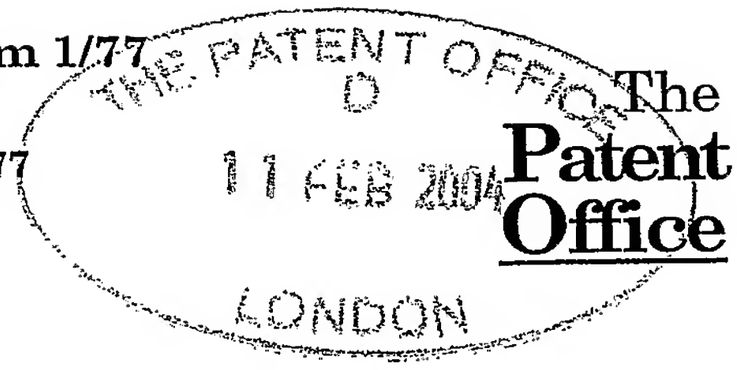
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Berry

Dated 3 December 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)



The **Patent Office**

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales NP10 8QQ

1. Your reference **4-33647P1**

12FEB04 E872576-3 D00245
P01/7700 0.00-0403038.3 ACCOUNT CHA

2. Patent application number
(The Patent Office will fill in this part) 0403038.3

3. Full name, address and postcode of the or of each applicant
(underline all surnames)

07125487005

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

SWITZERLAND

4. Title of invention

Organic Compounds

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)*

Craig McLean
Novartis Pharmaceuticals UK Limited
Patents and Trademarks
Wimblehurst Road
Horsham, West Sussex
RH12 5AB
07181522002 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	112
Claim(s)	13
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	/
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature — Date

Craig McLean — **11th February 2004**

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew — **(01403) 323069**

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

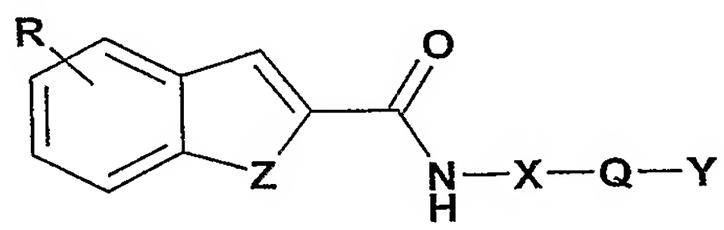
d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

Organic Compounds

The invention relates to bicyclic carbonyl amino derivatives which are antagonists of Chemokine Receptor 2 (CCR-2) and Chemokine Receptor 5 (CCR-5), and to their use in the treatment of diseases and disorders which involve migration and activation of monocytes and T-cells, including inflammatory diseases.

Accordingly the invention in a first aspect provides a compound of formula (I), or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

Wherein:

Z is CR_1R_2, NR_3, O or S;

R represents one or more ring substituents selected from the group consisting of H, hydroxy, an optionally substituted lower alkoxy, lower alkenoxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl-lower alkoxy or heteroaryl-lower alkoxy, an optionally substituted lower alkyl or lower alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group;

R_1, R_2, and R_3 are independently selected from the group consisting of H and lower alkyl;

X is a C_3-C_{18} cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which may be optionally substituted;

Q is a linker of between 1 and 3 atoms in length;

Y is C_3-C_{18} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocyloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

The optional substituent or substituents on R are independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

The optional substituent or substituents on X are independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

The optional substituent or substituents on Y are independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

For the avoidance of doubt, the terms listed below are to be understood to have the following meaning throughout the present description and claims:

The term "lower", when referring to organic radicals or compounds means a compound or radical with may be branched or unbranched with up to and including 7 carbon atoms.

A lower alkyl group may be branched, unbranched or cyclic and contains 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl represents, for example: methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl or 2,2-dimethylpropyl.

A lower alkoxy group may be branched or unbranched and contains 1 to 7 carbon atoms, preferably 1 to 6 carbon atoms. Lower alkoxy represents, for example: methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy. Lower alkoxy includes cycloalkyloxy and cycloalkyl - lower alkyloxy.

A lower alkene, alkenyl or alkenoxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1 to 4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene, lower alkenyl or lower alkenyloxy represents for example vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl and the oxy equivalents thereof.

In the present application, oxygen containing substituents, e.g. alkoxy, alkenyloxy, alkynyloxy, carbonyl, etc. encompass their sulphur containing homologues, e.g. thioalkoxy, thioalkenyloxy, thioalkynyloxy, thiocarbonyl, sulphone, sulphoxide etc.

Halo or halogen represents chloro, fluoro, bromo or iodo.

Aryl represents carbocyclic aryl, heterocyclic aryl or biaryl.

Carbocyclic aryl is an aromatic cyclic hydrocarbon containing from 6 to 18 ring atoms. It can be monocyclic, bicyclic or tricyclic, for example naphthyl, phenyl, or phenyl mono-, di- or trisubstituted by one, two or three substituents.

Heterocyclic aryl is an aromatic monocyclic or bicyclic hydrocarbon containing from 5 to 18 ring atoms one or more of which are heteroatoms selected from O, N or S. Preferably there are one or two heteroatoms. Heterocyclic aryl represents, for example: pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl,

benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl. Heterocyclic aryl also includes such substituted radicals.

Cycloalkyl represents a cyclic hydrocarbon containing from 3 to 12 ring atoms preferably from 3 to 6 ring atoms. Cycloalkyl represents, for example: cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The cycloalkyl may optionally be substituted.

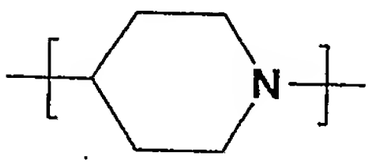
Heterocycloalkyl represents a mono-, di- or tricyclic hydrocarbon which may be saturated or unsaturated and which contains one or more, preferably one to three heteroatoms selected from O, N or S. Preferably it contains between three and 18 ring atoms. The term heterocycloalkyl is intended also to include bridged heterocycloalkyl groups such as 3-hyroxy-8-aza-bicyclo[3.2.1]oct-8-yl.

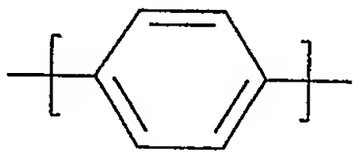
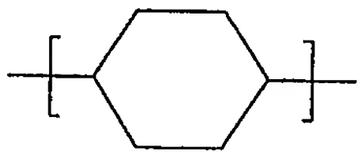
Pharmaceutically acceptable prodrug esters are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acid of formula (I). Such esters are for example lower alkyl esters (such as methyl or ethyl esters), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester).

Referring to formula (I), preferably Z is NH, NCH_3, CH_2, S or O.

R is preferably hydroxy, an optionally substituted lower alkoxy, alkenoxy, cycloalkyl-lower alkyloxy, aryloxy, heteroaryloxy, aryl-lower alkyloxy or heteroaryl lower alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group; preferably R is located on the 4 position of the ring;

X is preferably selected from the group consisting of:



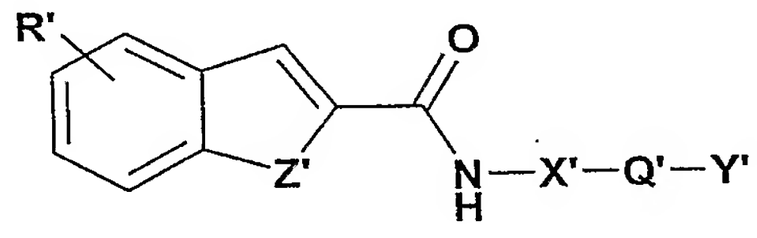
,  ,  ;

Q is preferably defined by $-CR_4R_5-$ or $-CR_4R_5-Q_1-$ wherein Q_1 denotes $-CR_6R_7-$ or $-NR_8-$; R_4, R_5, R_6 and R_7 and R_8 being independently selected from the group consisting of H, an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted aryl or an optionally substituted aryl-lower alkyl group, for example methyl, $(CH_3)_2CH-CH_2-$, $CH_3-C(=CH_2)-CH_2-$, $(CH_3)_3C-CH_2-$, benzyl;

Q is more preferably selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y is preferably selected from the group consisting of: piperidinyl, azepanyl, azocanyl, phenyl, tetrahydropyranyl, 8-aza-bicyclo[3.2.1]oct-8-yl, tetrahydropyridinyl, octahydroquinolizinyl, each of which is optionally substituted. Preferred optional substituents for Y are: hydroxy, amino, halo.

A second aspect of the invention provides a compound of formula (II), or a pharmaceutically acceptable salt, ester or prodrug thereof:



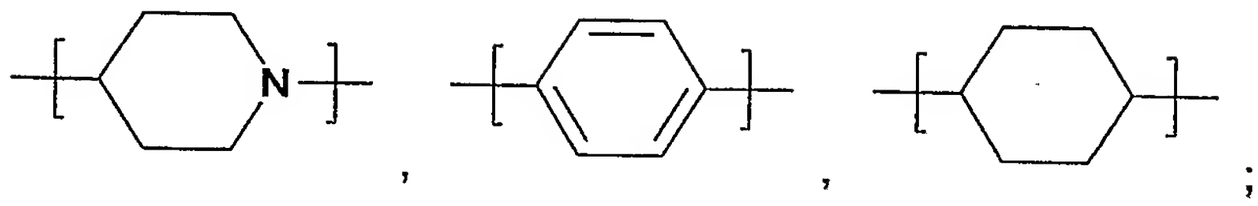
(II)

wherein:

Z' is NH, NCH_3, CH_2, S or O.

R' is hydroxy, an optionally substituted lower alkoxy, cycloalkyl-lower alkyloxy, aryloxy, heteroaryloxy or aryl-lower alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group;

X' is selected from the group consisting of:



Q' is selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y' is selected from the group consisting of: optionally substituted piperidinyl, azepanyl, azocanyl, phenyl, tetrahydropyranyl, 8-aza-bicyclo[3.2.1]oct-8-yl, tetrahydropyridinyl, each of which is optionally substituted;

Preferred compounds of formula I are:

5-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

6-Methoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

4,6-Dimethoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide-dihydrochloride

5,6-Dimethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

6-Benzyloxy-5-methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-cyclohexyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide

5-Hydroxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

6-Hydroxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

5-(2-Methyl-allyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

6-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

6-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-azepann-1-yl-ethyl)piperidin-4-yl]-amide

4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2R-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2S-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1R-methyl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1S-methyl-ethyl)-piperidin-4-yl]-amide

7-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

5-Methoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

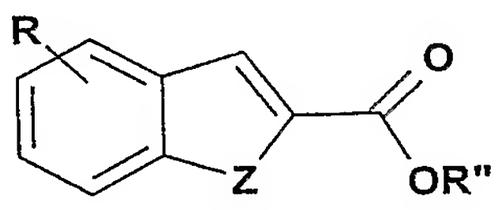
5-Hydroxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Isobutoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

According to a third aspect of the invention there is provided a compound of formula (I) for use as a pharmaceutical for the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

According to a fourth aspect of the invention there is provided a process for the preparation of a compound of formula (I) comprising:

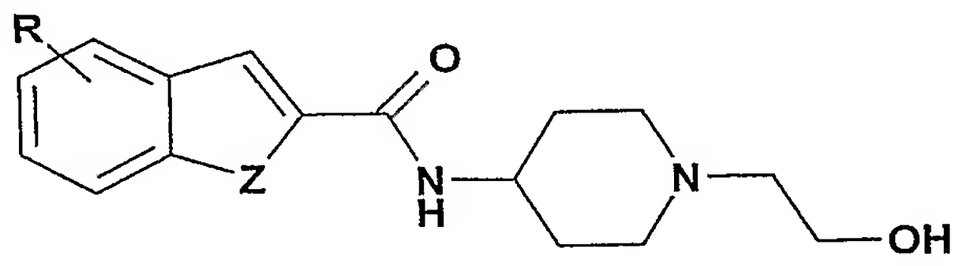
(a) reacting a compound of formula (III):



(III)

wherein R" is H or a lower alkyl group, with a compound of formula NH_2-X-Q-Y, the groups R, Z, X, Q and Y being defined above; or

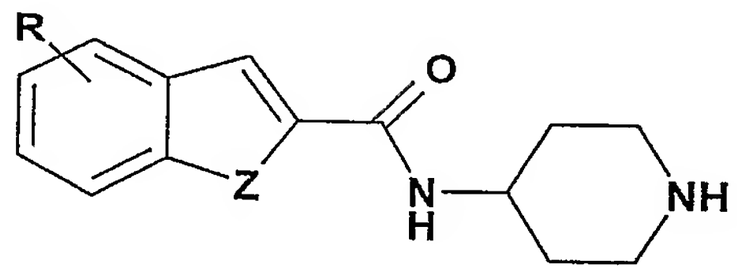
(b) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is $-CH_2-CH_2-$, and Y is a group having the formula $-NR_7R_8$ wherein N, R_7 and R_8 are linked to define collectively a heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, heteroaryl, or fused aryl-heterocycloalkyl, reacting a compound of formula (IV):



(IV)

with a compound of formula NHR_7R_8, wherein R_7 and R_8 are as defined above, and R and Z are as defined earlier; or

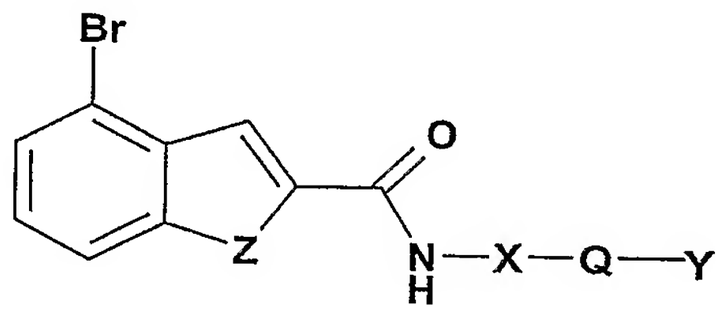
(c) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is CH_2-, reacting a compound of formula (V):



(V)

in which R and Z are as defined above, with a compound of formula HO-CH_2-Y, in which Y is as defined earlier; or

(d) for the preparation of compounds of formula (I) wherein R represents one or more ring substituents as defined in claim 1 and wherein one of said substituents is an optionally substituted aryl group and is located at the 4 position of the ring, appropriately substituting the Br group in a compound of formula (VI) for said substituted aryl group:



(VI)

wherein Z, X, Q and Y are as earlier defined;

and recovering the resultant compounds of formula (I) in free or salt form.

The process of the invention is effected in conventional manner.

Process variant (a) is a condensation reaction between acid or ester and amine. It is conveniently effected by reacting the acid with the amine in the presence of coupling agents, for example TBTU/DIEA in a solvent such as DMF, or by reacting the ester with the amine in the presence of a coupling agent such as HOBT/EDC.

Process variant (b) is a condensation reaction which is conveniently carried out using a reagent such as cyanomethyl-triphenyl phosphonium iodide and Hunig's base.

Process variant (c) is a condensation reaction is also a condensation reaction which is conveniently carried out using a reagent such as cyanomethyl-triphenyl phosphonium iodide and Hunig's base.

Process variant (d) is a substitution reaction and is conveniently effected using the appropriate aryl-boronic acid and triphenylphosphine in the presence of lead (II) acetate.

The compounds of the invention can be recovered from the reaction mixture and purified in conventional manner. Isomers, such as enantiomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active, starting materials.

The starting materials and intermediates are either known or can be prepared according to known methods or analogously as described in the Examples.

According to a fifth aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) in association with a pharmaceutically acceptable diluent or carrier.

According to a sixth aspect of the invention there is provided the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of an autoimmune or inflammatory disease or condition.

According to a seventh aspect of the invention there is provided a method of inhibiting chemokine receptors or macrophage proteins or of reducing inflammation in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula (I).

According to an eighth aspect of the invention there is provided a method of treating an inflammatory or autoimmune disease or condition, comprising administering to said subject an effective amount of a compound of formula (I).

Agents of the invention may be prepared by processes described below:

EXPERIMENTAL SECTION

Abbreviations:

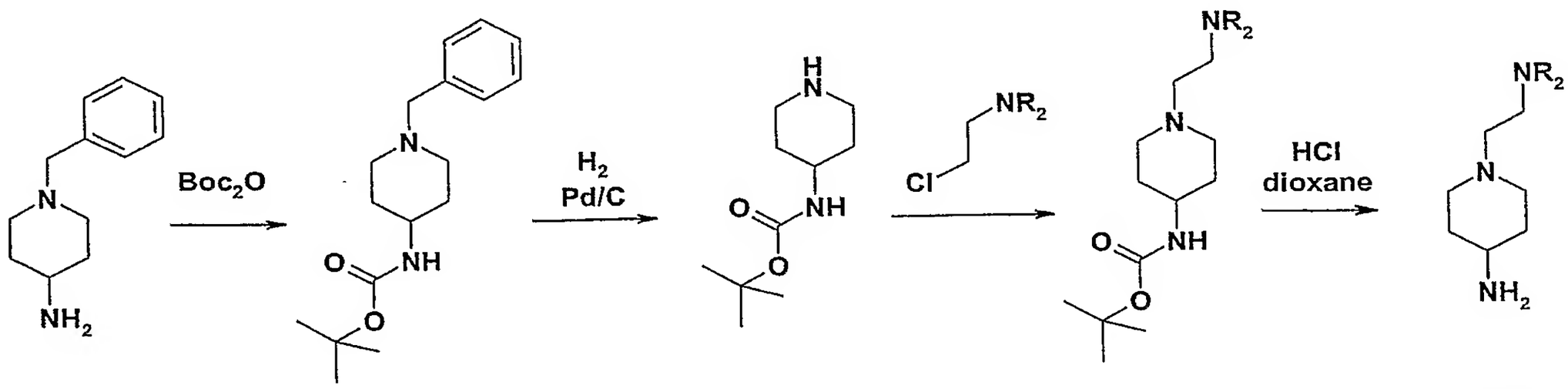
BOC:	t-Butyloxycarbonyl
Boc2O:	Di-t-butyl dicarbonate
DCC:	Dicyclohexyl-carbodiimide
DCE:	Dichloroethane
DCM:	Dichloromethane
DEAD:	Diethyl azadicarboxylate
DIEA:	Ethyl-diisopropyl-amine
DMAP:	Dimethyl-pyridin-4-yl-amine
DME:	1,2-Dimethoxy-ethane
DMF:	N,N-Dimethyl formamide
EDC:	(3-Dimethylamino-propyl)-ethyl-carbodiimide hydrochloride
Ether:	Ethoxy-ethane
EtOH:	Ethanol
EtOAc:	Acetic acid ethyl ester
HCl:	Hydrochloric acid
HOBT:	Benzotriazol-1-ol
LAH:	Lithium aluminumhydride
LDA:	Lithium diisopropylamine
MeOH:	Methanol
NaOH:	Sodium hydroxide
NMP:	1-Methyl-pyrrolidin-2-one
Pd/C:	Palladium on carbon
TBAF:	Tetrabutylammonium fluoride
TBME:	t-Butyl-methyl ether
TBDMS:	t-Butyl-dimethyl-silyl
TBTU	O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
t-BuOH	2-Methyl-propan-2-ol
TFA:	Trifluoro-acetic acid
THF:	Tetrahydrofuran

1H-NMR spectra are recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and number of protons. Electron Spray Ionization (ESI) mass spectra are recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge. Preparative HPLC purifications are performed with XTerraTM RP18 19x150mm columns, using acetonitrile/water or MeOH/water as eluent systems. All reagents, starting materials and intermediates utilized in these examples are available from commercial sources or are readily prepared by methods known to those skilled in the art. In the following examples all temperatures are in degrees Celcius and are uncorrected.

Synthesis of the amine building blocks

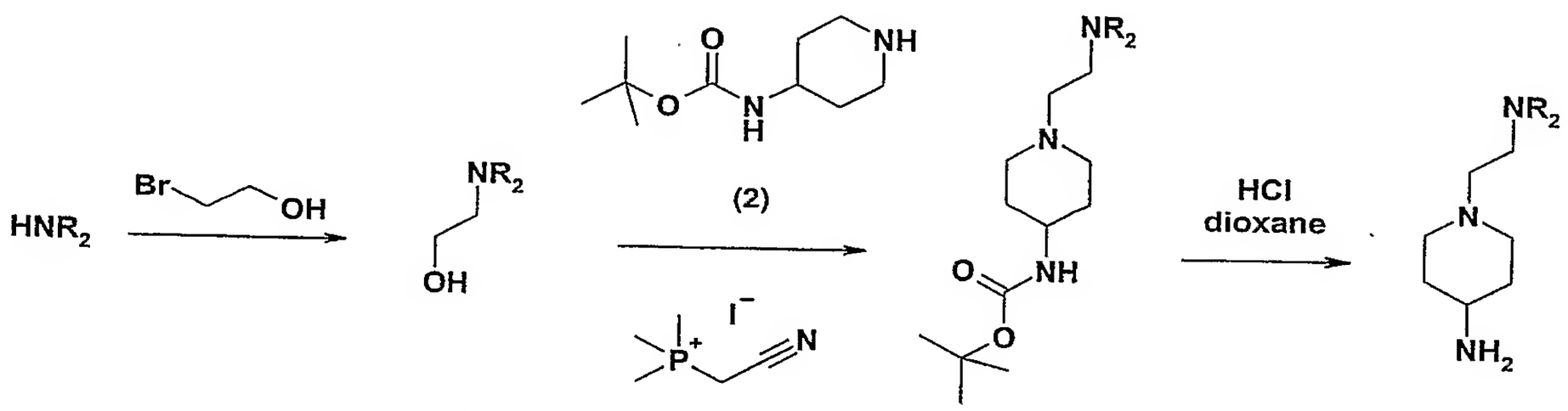
The amines **4**, **6**, **9**, **12**, **15** **17**, **19**, **22**, **24**, **26** are prepared according the reaction schemes outlined below.

Reaction Scheme 1:



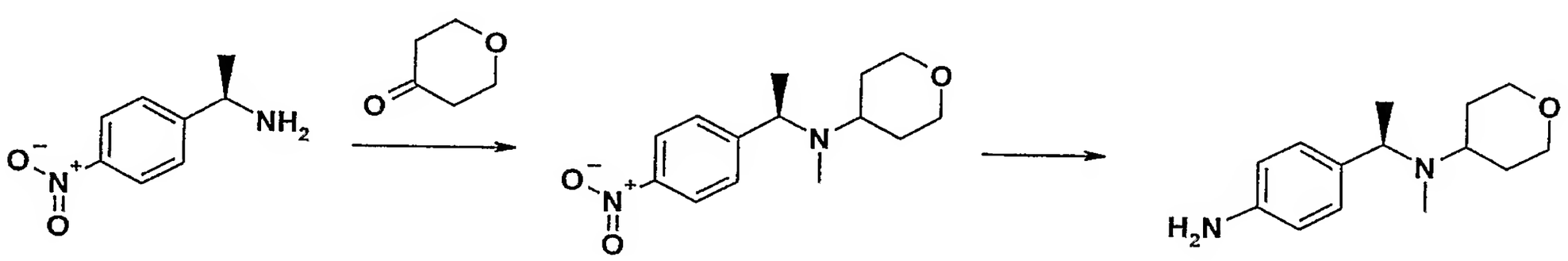
(1) (2) (3), (5) (4), (6)

Reaction Scheme 2:



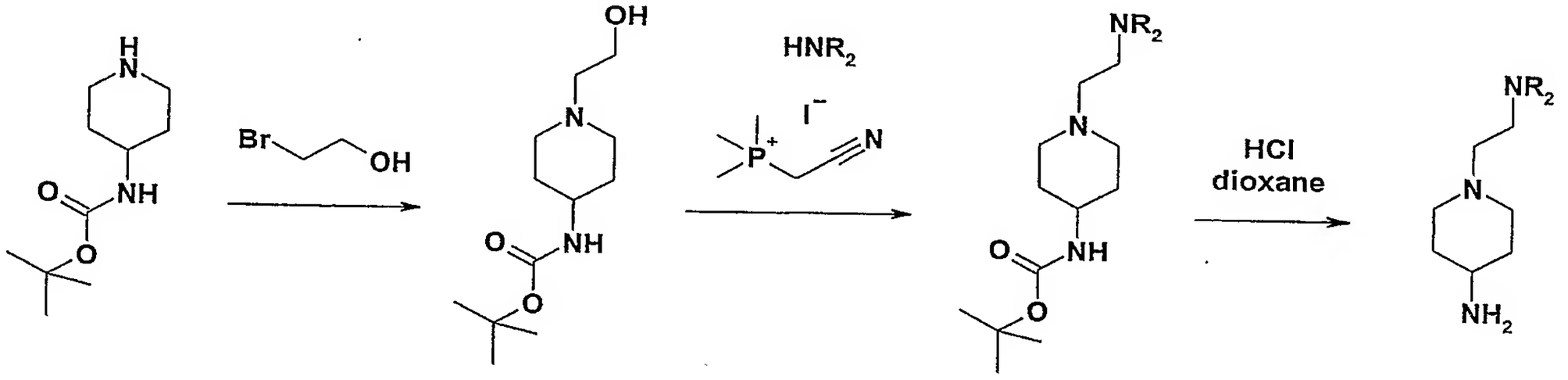
(7), (10), (13) (8), (11), (14) (9), (12), (15)

Reaction Scheme 3:



(16) (17)

Reaction Scheme 4:



(2) (18) (19), (21), (23) (20), (22), (24)

(1) (1-Benzyl-piperidin-4-yl)-carbamic acid tert-butyl ester (**1**)

1-Benzyl-piperidin-4-ylamine (50 g, 262.76 mmol) is dissolved in a mixture of 200 ml of water, 145 ml of 2 molar aqueous sodium hydroxide and 350 ml of t-BuOH at 0°C. A solution

of Boc2O (63.1 g, 1.1 equivalents) in 150 ml of t-BuOH is added dropwise within one hour at 0°C. A white suspension is formed which is allowed to stir overnight at room temperature. The reaction mixture is diluted with ether and washed with water. The organic layers are dried over anhydrous sodium sulfate and evaporated under reduced pressure.
MS (ESI): 291 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.2–7.35 (m, 5H), 6.77 (br d, 1H), 3.44 (s, 2H), 3.22 (br m, 1H), 2.75 (m, 2H), 1.95 (dt, 2H), 1.68 (m, 2H), 1.38 (s, 9H), 1.36 (dt 2H).

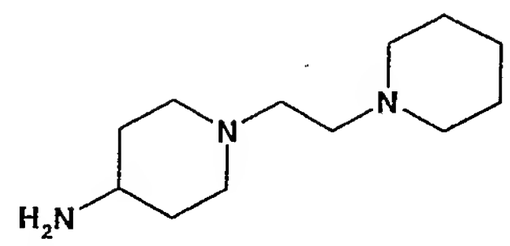
(2) Piperidin-4-yl-carbamic acid tert-butyl ester (**2**)

A solution of the ester **1** from above (66 g, 227.27 mmol) in 1 l of ethanol is hydrogenated under normal pressure with 10 g of Pd/C (10%) for 16 hours at room temperature. The mixture is filtered over celite and evaporated under reduced pressure. Recrystallisation from ether gives white crystals.
MS (ESI): 201 $[M+H]^+$, 401 [2M+H]+, 1H-NMR (DMSO-d_6): δ (ppm) 6.7 (br d, NH), 3.22 (br m, 1H), 2.88 (dt, 2H), 2.39 (dt, 2H), 1.8 (br s, NH), 1.6 (dt, 2H), 1.35 (s, 9H), 1.18 (dt, 2H).

(3) 1-(2-Piperidin-1-yl-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (**3**)

Piperidin-4-yl-carbamic acid tert-butyl ester (**2**) (4.8 g, 23.72 mmol), 1-(2-Chloro-ethyl)-piperidine hydrochloride (5.3 g, 26.09 mmol) and DIEA (8.9 ml, 52.18 mmol) are dissolved in 150 ml of chloroform and refluxed for 18 hours. After addition of more 1-(2-Chloro-ethyl)-piperidine hydrochloride (2.65 g, 13.05 mmol) and DIEA (4.4 ml, 26.09 mmol) the reaction mixture is refluxed for another 4 hours. After cooling to room temperature, the mixture is diluted with DCM and washed with water and 5% aqueous sodium hydrogen carbonate solution. Evaporation gives brownish crystals which are recrystallized from ether/hexane.
MS (ESI): 312 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.3-2.4 (m, 8H), 1.92 (dt, 2H), 1.65 (m, 2H), 1.48 (m, 4H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

(4) 1-(2-Piperidin-1-yl-ethyl)-piperidin-4-ylamine (**4**)



Ester **3** from above (5.2 g, 16.7 mmol) is suspended at 0°C in 60 ml of a 4M solution of HCl in dioxane and stirred at room temperature for 3 hours. After evaporation under reduced pressure the crude product is dried at high vacuum.

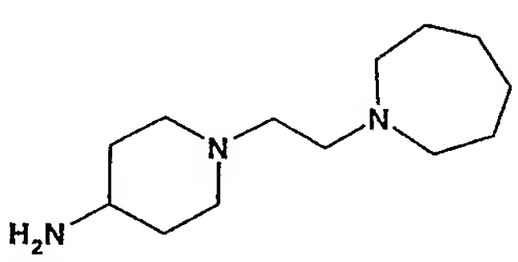
MS (ESI): 212 $[M+H]^+$, 1H-NMR (D2O): δ (ppm) 4.14 (m, 2H), 4.04 (br m, 5H), 3.8 (m, 4H), 3.65 (dt, 2H), 2.85 (d, 2H), 2.45 (m, 2H), 2.35 (m, 4H), 2.15 (m, 2H).

(5) [1-(2-Azepan-1-yl-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (**5**)

It is synthesized analogous to ester **3** starting from 2-(hexamethylenimino)ethyl chloride (13.8 g) and ester **2** (12.4 g).

MS (ESI): 326 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.3-2.6 (m, 8H), 1.95 (dt, 2H), 1.65 (m, 2H), 1.55 (m, 6H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

(6) 1-(2-Azepan-1-yl-ethyl)-piperidin-4-ylamine (**6**)



It is prepared analogous to **4** starting from ester **5** (14 g).

MS (ESI): 226 $[M+H]^+$, 1H-NMR (120°C, DMSO-d_6): δ (ppm) 8.5 (br, NH3+), 3.5 (m, 5H), 3.4 (m, 2H), 3.3 (m, 4H), 2.97 (m, 2H), 2.18 (m, 2H), 2.05 (m, 2H), 1.9 (m, 4H), 1.7 (m, 4H).

(7) 1-(2-Hydroxy-ethyl)-piperidin-4-ol (**7**)

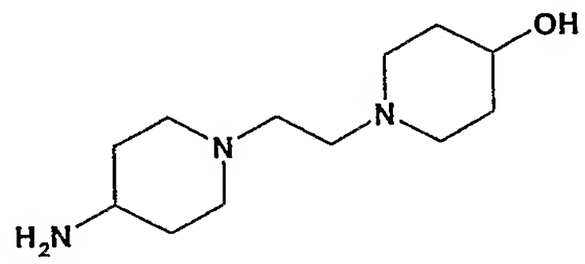
Piperidin-4-ol (5 g, 49.4 mmol) is dissolved in 200 ml of ethanol and anhydrous sodium carbonate (21 g, 197.6 mmol) is added. 2-Bromo-ethanol (6.9 ml, 98.8 mmol) is added dropwise and the reaction mixture is refluxed for 16 hours. After evaporation under reduced

pressure the mixture is stirred with 200 ml of DCM and filtered. The clear filtrate is evaporated under reduced pressure und dried at high vacuum.
MS (ESI): 146 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.52 (d, 1H), 4.32 (t, 1H), 3.48 (dt, 2H), 3.4 (m, 1H), 2.7 (m, 2H), 2.35 (t, 2H), 2.05 (m, 2H), 1.68 (m, 2H), 1.3-1.4 (m, 2H).

(8) {1-[2-(4-Hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**8**)

Piperidin-4-yl-carbamic acid tert-butyl ester **2** (5 g, 25 mmol), 1-(2-Hydroxy-ethyl)-piperidin-4-ol **7** (4 g, 27.5 mmol) and DIEA (5.6 ml, 32.5 mmol) are suspended in 25 ml of propionitril. Cyanomethyl-trimethyl-phosphonium iodide (4 g, 30 mmol) is added and the reaction mixture is refluxed. Additional portions of cyanomethyl-trimethyl-phosphonium iodide (1.5 g, 11.25 mmol) are added after 90 minutes and after 3 hours. After cooling to room temperature, a solution of potassium carbonate (4 g) in 250 ml of water is added and the product is isolated by extraction with DCM. Evaporation under reduced pressure gives 6.9 g of a red oil which could be crystallized from ether.
MS (ESI): 328 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.72 (br d, 1H), 4.5 (d, 1H), 3.42 (m, 1H), 3.2 (m, 1H), 2.8 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.0 (dt, 2H), 1.9 (dt, 2H), 1.68 (m, 4H), 1.4 (s, 9H), 1.35 (m, 4H).

(9) 1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-4-ol tri-hydrochloride (**9**)



Ester **8** (2.2 g, 6.72 mmol) is dissolved in 4M HCl in dioxane at 0°C and stirred at room temperature for 3 hours. After evaporation of the solvent the product is dried at high vacuum.
MS (ESI): 228 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 5 (m, 1H), 3.4 (m, 4H), 2.7 (m, 4H), 2.4 (m, 2H), 1.85-2.0 (m, 4H), 1.65 (m, 4H), 1.35 (m, 4H), 1.2 (m, 2H).

(10) 8-(2-Hydroxy-ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol (**10**)

8-Aza-bicyclo[3.2.1]octan-3-ol hydrochloride (5.1 g, 31.45 mmol)) and sodium carbonate (13.3 g, 125.8 mmol) are suspended in 150 ml of ethanol at room temperature. 2-Bromo-ethanol (4.4 ml, 62.9 mmol) is added dropwise within 20 minutes and the reaction mixture is refluxed for 15 hours. After cooling to room temperature the reaction mixture is evaporated under reduced pressure. The mixture is stirred with 200 ml of DCM and filtered. The clear filtrate is dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure und dried at high vacuum.

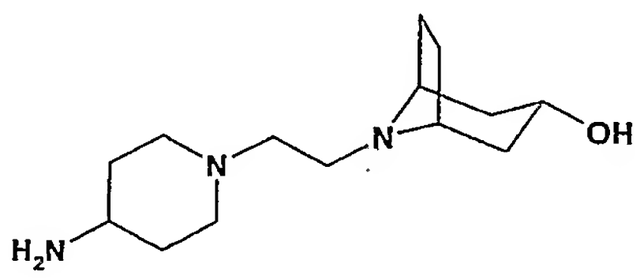
MS (ESI): 172 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.25 (d, 2H), 3.78 (t, 1H), 3.42 (t, 2H), 3.06 (m, 2H), 2.36 (t, 2H), 2.03 (m, 2H), 1.85 (m, 2H), 1.75 (m, 2H), 1.55 (d, 2H).

(11) {1-[2-(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**11**)

Piperidin-4-yl-carbamic acid tert-butyl ester **2** (1 g, 5 mmol), 8-(2-hydroxy-ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol **10** (1 g, 5.5 mmol) and DIEA (1.1 ml, 6.5 mmol) are dissolved in 5 ml of propionitril. Cyanomethyl-trimethyl-phosphonium iodide (792 mg, 6 mmol) is added under stirring and the reaction mixture is refluxed and followed by TLC. Additional cyanomethyl-trimethyl-phosphonium iodide (400 mg) is added after 2 hours and the mixture is refluxed for another hour. After cooling to room temperature, DCM. The combined organic layers are washed with brine, dried over anhydrous a solution of potassium carbonate (4 g) in 250 ml of water is added and the product is isolated by extraction with sodium sulfate, filtered and evaporated under reduced pressure. The crude product (1.9 g) is crystallized from ether.

MS (ESI): 354 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 4.25 (d, OH), 3.8 (m, 1H), 3.17 (m, 1H), 3.08 (m, 2H), 2.8 (m, 2H), 2.35 (m, 4H), 2.0 (m, 2H), 1.92 (m, 2H), 1.85 (dt, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.53 (m, 2H), 1.38 (s, 9H), 1.33 (m, 2H).

(12) 8-[2-(4-Amino-piperidin-1-yl)-ethyl]-8-aza-bicyclo[3.2.1]octan-3-ol (**12**)



Ester **11** (4.5 g, 12.73 mmol) is dissolved in 4M HCl in dioxane at 0°C and stirred at room temperature for 3 hours. After evaporation of the solvent the product is dried at high vacuum.
MS (ESI): 254 $[M+H]^+$.

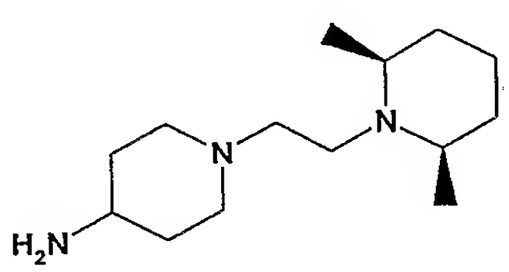
(13) 2-(2,6-Dimethyl-piperidin-1-yl)-ethanol (**13**)

Compound **13** is prepared analogous to **10** starting from cis-2,6-dimethylpiperidin (6.4 ml, 44.17 mmol) and bromethanol (6.1 ml, 88.33 mmol).
MS (ESI): 158.1 $[M+H]^+$]+, 1H-NMR (DMSO-d_6): δ (ppm) 4.48 (br, 1H), 3.4 (t, 2H), 2.6 (t, 2H), 2.4 (m, 2H), 1.1-1.6 (m, 6H), 1.03 (d, 6H).

(14) {1-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**14**)

Compound **14** is prepared analogous to **11** starting from compound **13** (3.85 g, 24.48 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester **2** (4.46 g, 22.25 mmol).
MS (ESI): 340.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 3.18 (m, 1H), 2.75 (m, 2H), 2.65 (m, 2H), 2.35 (m, 2H), 2.25 (m, 2H), 1.92 (m, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.49 (m, 2H), 1.38 (s, 9H), 1.35 (m, 2H), 1.12 (m, 2H), 1.03 (d, 6H).

(15) 1-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine (**15**)



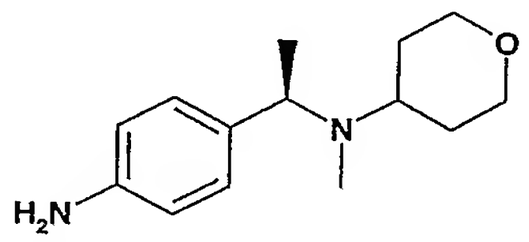
Compound **15** is prepared analogous to **12** starting from the BOC protected derivative **14** (6.16 g, 18.14 mmol).
MS (ESI): 240.3 $[M+H]^+$.

(16) Methyl-[(R)-1-(4-nitro-phenyl)-ethyl]-(tetrahydro-pyran-4-yl)-amine (**16**)

(R)-α-Methyl-4-nitro-benzylammonium hydrochloride (Aldrich, 3 g, 15 mmol), tetrahydropyridon (1.5 g, 15 mmol), pyridine (1.2 ml, 15 mmol) are dissolved in 100 ml DCE.

Sodium triacetoxyborohydride (4 g, 19 mmol, 95%) is added under stirring at room temperature; after 18 hours reaction time formaldehyde (2.4 ml, 30% in water) is added followed by sodium triacetoxyborohydride (3 g, 14 mmol, 95%) and the mixture is again stirred for 18 hours at room temperature. After addition of 2m HCl the product is isolated by distribution between aqueous ammonia and EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product is used without further purification.
MS (ESI): 265 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.20 (d, 2H), 7.55 (d, 2H), 4.0 (br m, 2H), 3.95 (br m, 1H), 3.3 (br m, 2H), 2.7 (br m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.40 (d, 3H)

(17) [(R)-1-(4-Amino-phenyl)-ethyl]-methyl-(tetrahydro-pyran-4-yl)-amine (**17**)



Methyl-[(R)-1-(4-nitro-phenyl)-ethyl]-(tetrahydro-pyran-4-yl)-amine **16** from above (3.2 g, 12 mmol) is stirred with RaNi (1 g) in 100 ml of MeOH. Hydrazine monohydrate (3.2 ml) is added dropwise at room temperature and the reaction mixture is stirred for further 3 hours. After filtration and evaporation under reduced pressure the product is isolated by distribution between Et2O and brine, drying the organic phase with sodium sulfate, filtration and evaporation as yellow oil.
MS (ESI): 235 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.15 (d, 2H), 6.65 (d, 2H), 4.0 (br m, 2H), 3.7 (br m, 1H), 3.6 (NH2), 3.3 (br m, 2H), 2.7 (br m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.30 (d, 3H)

(18) [1-(2-Hydroxy-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (**18**)

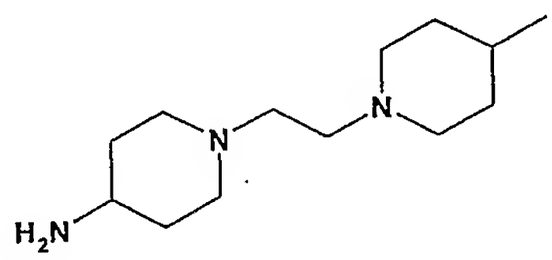
To a solution of piperidin-4-yl-carbamic acid tert-butyl ester **2** (10 g, 50 mmol) in 100 ml of methanol are added sodium carbonate (21.2 g, 200 mmol) and 2-bromoethanol (7.1 ml, 100 mmol). The mixture is stirred over night. The solvents are then evaporated and the residue is triturated with DCM, filtered and evaporated again. The crude product is purified by chromatography using EtOAc/MeOH (saturated with ammonia) : 9/1.

MS (ESI): 245.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, 1H), 4.34 (t, 1H), 3.46 (q, 2H), 3.19 (br m, 1H), 2.8 (m, 2H), 2.35 (t, 2H), 1.95 (m, 2H), 1.66 (m, 2H), 1.39 (s, 9H), 1.35 (m, 2H).

(19) {1-[2-(4-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**19**)

A mixture of ester **18** (3 g, 12.28 mmol), 4-methyl piperidine (1.46 ml, 12.28 mmol) and DIEA (2.7 ml, 15.96 mmol) in 30 ml of propionitrile is treated with solid cyanomethyl-trimethyl-phosphonium iodide (3.58 g, 14.74 mmol) and heated at reflux for 3 hours. After cooling to room temperature, a 2M-K2CO3 solution is added until basic and the mixture is extracted twice with DCM. The organic layers are washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude material is purified by chromatography using EtOAc/MeOH (saturated with ammonia) : 9/1.
MS (ESI): 326.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.74 (br d, 1H), 3.16 (m, 1H), 2.78 (m, 4H), 2.33 (br s, 4H), 1.86 (m, 4H), 1.64 (m, 2H), 1.53 (m, 2H), 1.36 (s, 9H), 1.32 (m, 3H), 1.08 (m, 2H), 0.86 (d, 3H).

(20) 1-[2-(4-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (**20**)

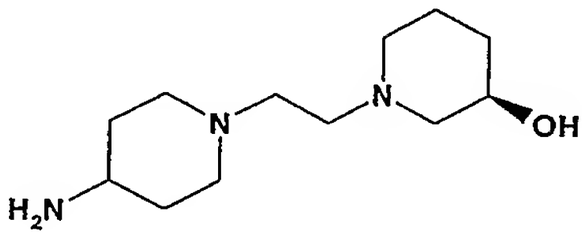


The tert-butyl ester **19** (2 g, 6.14 mmol) is suspended in 10 ml of dioxane. DCM is then added until the solid dissolved. To this mixture, 4M-HCl in dioxane (12.3 ml, 49.2 mmol) is added. After stirring over night the solvents are evaporated to leave a white solid product.
MS (ESI): 226.2 $[M+H]^+$

(21) {1-[2-((R)-3-Hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**21**)

It is prepared analogous to **19** starting from tert-butyl ester **18** (3.52 g, 14.41 mmol), (R)-3-hydroxy-piperidine hydrochloride (2.18 g, 15.85 mmol), DIEA (5.6 ml, 33.14 mmol) and cyanomethyl-trimethyl-phosphonium iodide (4.2 g, 17.29 mmol).
MS (ESI): 328.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.61 (br d, 1H), 3.89 (m, 3H), 3.53 (m, 1H), 3.03 (m, 2H), 2.55-2.73 (m, 6H), 2.44 (m, 1H), 2.3 (m, 2H), 1.83-2.02 (m, 3H), 1.5-1.7 (m, 4H), 1.44 (s, 9H).

(22) 1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-(R)-3-ol (**22**)

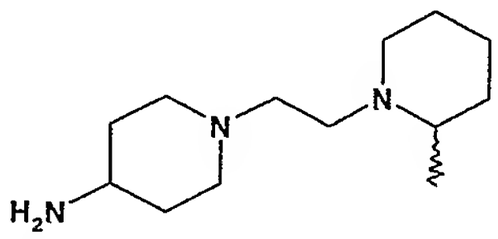


It is prepared by BOC-cleavage of tert-butyl ester **21** (1.7 g, 5.19 mmol) with 4M-HCl in dioxane (10.4 ml, 41.52 mmol) as described for amine **20**.
MS (ESI): 228.3 $[M+H]^+$

(23) {1-[2-((S)-2-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (**23**)

It is prepared analogous to **19** starting from tert-butyl ester **18** (2 g, 8.19 mmol), (S)-2-methyl-piperidine (0.985 ml, 8.19 mmol), DIEA (1.8 ml, 10.65 mmol) and cyanomethyl-trimethyl-phosphonium iodide (2.39 g, 9.83 mmol).
MS (ESI): 326.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.42 (br d, 1H), 3.47 (m, 1H), 2.84 (m, 4H), 2.47 (m, 3H), 2.15-2.35 (m, 2H), 2.1 (m, 2H), 1.92 (m, 2H), 1.2-1.75 (m, 8H), 1.44 (s, 9H), 1.08 (d, 3H).

(24) 1-[2-((RS)-2-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine (**24**)



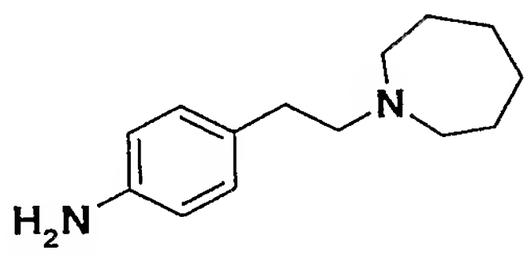
It is prepared by BOC-cleavage of tert-butyl ester **23** (1.3 g, 3.99 mmol) with 4M-HCl in dioxane (8 ml, 32 mmol) as described for amine **20**.

MS (ESI): 226.2 $[M+H]^+$

(25) 1-[2-(4-Nitro-phenyl)-ethyl]-azepane (**25**)

1-(2-Bromo-ethyl)-4-nitro-benzene (10 g, 43.47 mmol) is added under argon to a mixture of azepane (4.9 ml, 43.47 mmol) and potassium carbonate (6 g, 43.47 mmol) in 100 ml of DMF. After stirring over night at room temperature, the mixture is filtered and evaporated under high vacuum. The residue is dissolved in ethyl acetate, washed with water and brine and dried over sodium sulfate. Evaporation gives a yellow oil.
MS (ESI): 247.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.15 (d, 2H), 7.55 (d, 2H), 2.87 (t, 2H), 2.73 (t, 2H), 2.65 (t, 4 H), 1.5 – 1.6 (m, 8H).

(26) 4-(2-Azepan-1-yl-ethyl)-phenylamine (**26**)

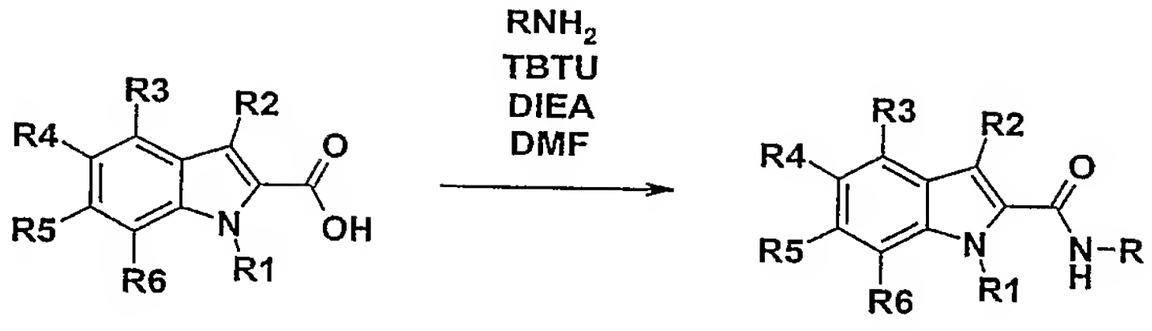


Compound **25** (9.1 g, 36.65 mmol) is hydrogenated for 3h at room temperature with palladium on carbon in 150 ml of ethanol and 18.3 ml of 4M aqueous hydrochloric acid. The mixture is filtered over celite and evaporated.
MS (ESI): 219 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 10.85 (br, 1H), 9.8 (br, 3H), 7.3 (m, 2H), 7.2 (m, 2H), 3.42 (m, 2H), 3.25 (m, 2H), 3.18 (m, 2 H), 3.08 (m, 2H), 1.85 (m, 4H), 1.68 (m, 2H), 1.58 (m, 2H).

Synthesis of the indole-2-carboxamides

The indole-2-carboxamides are generally prepared by a TBTU-mediated coupling of appropriately substituted indole-2-carboxylic acids with the corresponding amines in the presence of Hünig's base (Reaction Scheme 5).

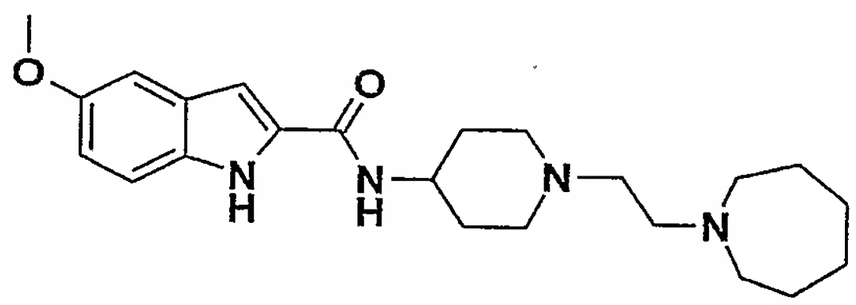
Reaction Scheme 5:



An illustrative example is given below.

Example 1

1. 5-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

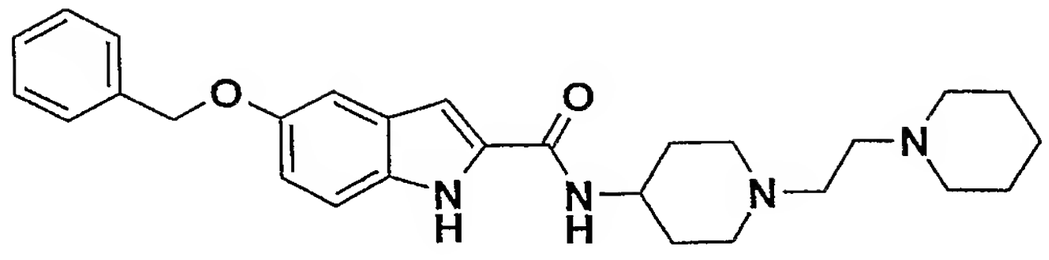


A solution of 5-Methoxy-1H-indole-2-carboxylic acid (1 g, 5.23 mmol), amine **6** (1.75 g, 5.23 mmol) and DIEA (2.7 ml, 15.69 mmol) in 20 ml of DMF is treated with solid TBTU (1.68 g, 5.23 mmol). The mixture is stirred over night and then evaporated. The crude residue is dissolved in EtOAc and washed twice with sodium bicarbonate (10%). The aqueous layers are re-extracted with DCM, the combined organic layers are washed with brine and dried over sodium sulfate. The crude product is then purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 2%).

MS (ESI): 399.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.16 (d, 1H), 7.3 (d, 1H), 7.06 (br s, 2H), 6.82 (dd, 1H), 3.76 (s, 3H), 3.4 (br m, 1H), 2.9 (m, 2H), 2.53-2.71 (m, 6H), 2.4 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.47-1.64 (m, 10H).

Example 2

1. 5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

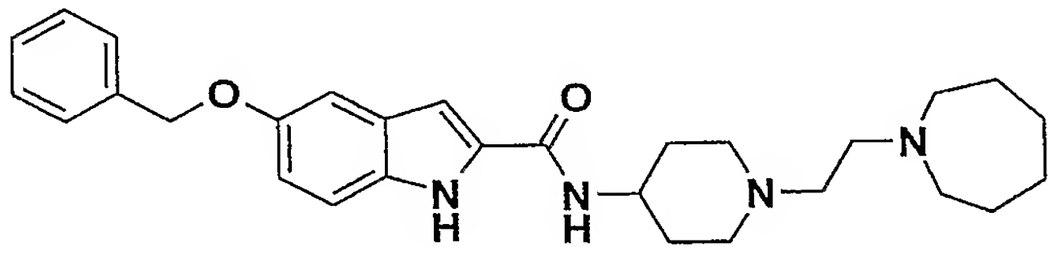


This compound is synthesized analogously to example 1 from 5-benzyloxy-1H-indole-2-carboxylic acid and amine **4**.

MS (ESI): 461.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, NH), 7.48 9d, 2H), 7.42 (m, 2H), 7.37 (m, 3H), 7.20 (d, 1H), 7.08 (s, 1H), 6.93 (dd, 1H), 5.12 (s, 2H), 3.82 (m, 1H), 3.02 (m, 2H), 2.82-2.60 (m, 8H), 2.30 (m, 2H), 1.85 (m, 2H, 1.62 (s, 2H), 1.48 (m, 2H).

Example 3

1. 5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

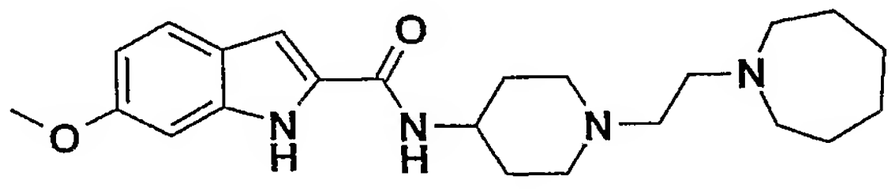


This compound is synthesized analogously to example 1 from 5-benzyloxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 475.4 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, NH), 8.19 (d, 1H), 7.50 (d, 2H), 7.42 (m, 2H), 7.36 (m, 2H), 7.19 (d, 1H), 7.07 (d, 1H), 6.92 (dd, 1H), 5.11 (s, 2H), 3.78 (m, 1H), 2.93 (m, 2H), 2.75-2.50 (m, 6H), 2.46 (m, 2H), 2.07 (m, 2H), 1.70 (m, 2H), 1.60 (m, 8H).

Example 4

1. 6-Methoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

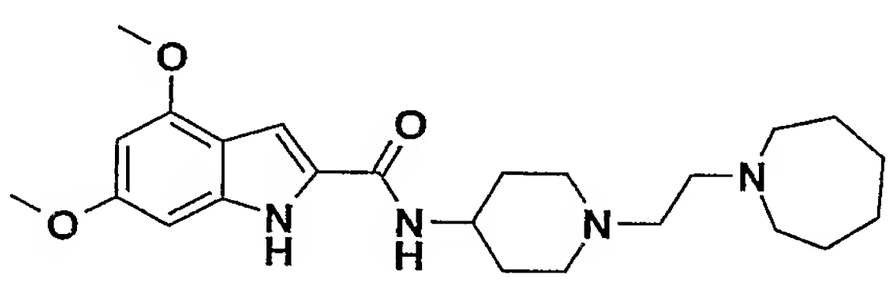


This compound is synthesized analogously to example 1 from 6-methoxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 399.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.2 (s, NH), 8.08 (d, NH), 7.46, d, 1H), 7.08 (bs, 1H), 6.88 (bs, 1H), 6.68 (dd, 1H), 3.76 (m, 1H), 2.89 (m, 2H), 2.60-2.50 (m, 4H), 2.38 (m, 2H), 2.02 (m, 2H), 1.55 (m, 12H).

Example 5

1. 4,6-Dimethoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide-dihydrochloride

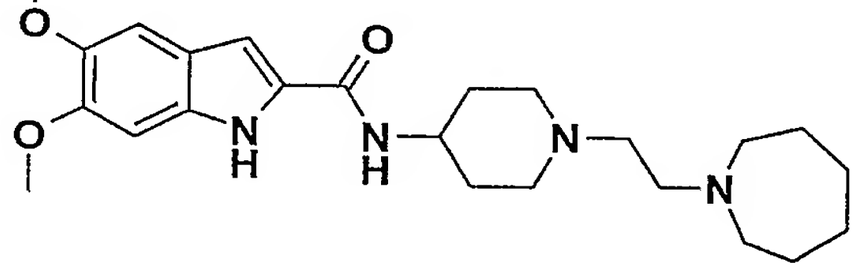


This compound is synthesized analogously to example 1 from 4,6-dimethoxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 429.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, NH), 10.75 (br, NH), 10.60 (br, NH), 8.41 (d, 1H), 7.20 (bs, 1H), 6.47 (s, 1H), 6.16 (s, 1H), 4.05 (m, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.75-3.45 (m, 6H), 3.15 (m, 2H), 2.10-1.50 (m, 10H).

Example 6

1. 5,6-Dimethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

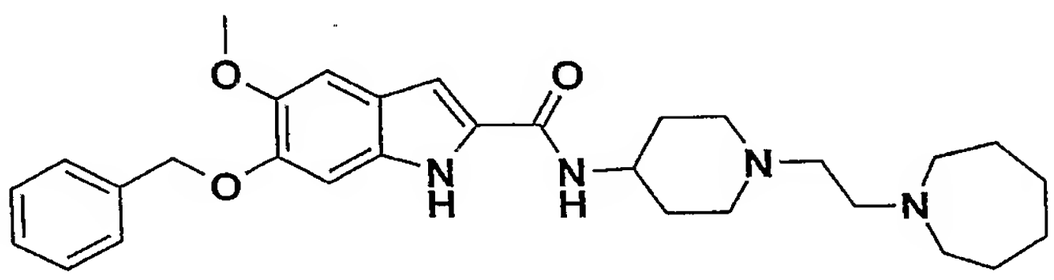


This compound is synthesized analogously to example 1 from 5,6-dimethoxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 429.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 10.25 (s, 1H), 8.06 (d, 1H), 7.06 (s, 1H), 7.02 (s, 1H), 6.98 (s, 1H), 3.75 (br s, 6H), 2.4-3.0 (br m, 9H), 2.09 (m, 2H), 1.79 (m, 2H), 1.47-1.69 (m, 10H).

Example 7

1. 6-Benzyloxy-5-methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

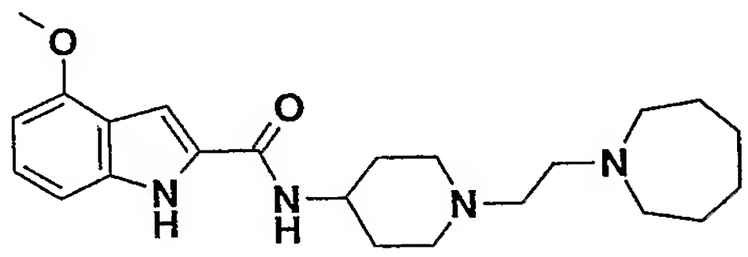


This compound is synthesized analogously to example 1 from 5-methoxy-6-benzyloxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 505.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.17 (s, 1H), 8.0 (d, 1H), 7.38-7.48 (m, 5H), 7.07 (s, 1H), 6.99 (d, 1H), 6.96 (s, 1H), 5.06 (s, 2H), 3.77 (s, 3H), 3.73 (m, 1H), 2.87 (m, 2H), 2.53-2.65 (m, 6H), 2.39 (m, 2H), 2.03 (m, 2H), 1.77 (m, 2H), 1.45-1.62 (m, 10H).

Example 8

1. 4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

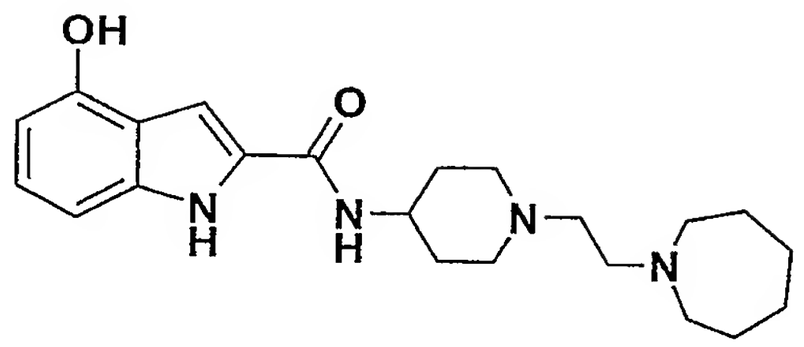


This compound is synthesized analogously to example 1 from 4-methoxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 399.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.24 (d, 1H), 7.28 (s, 1H), 7.09 (t, 1H), 7.0 (d, 1H), 6.5 (d, 1H), 3.75-3.9 (m, 4H), 2.92-3.25 (m, 8H), 2.73 (m, 2H), 2.27 (m, 2H), 1.52-1.9 (m, 12H).

Example 9

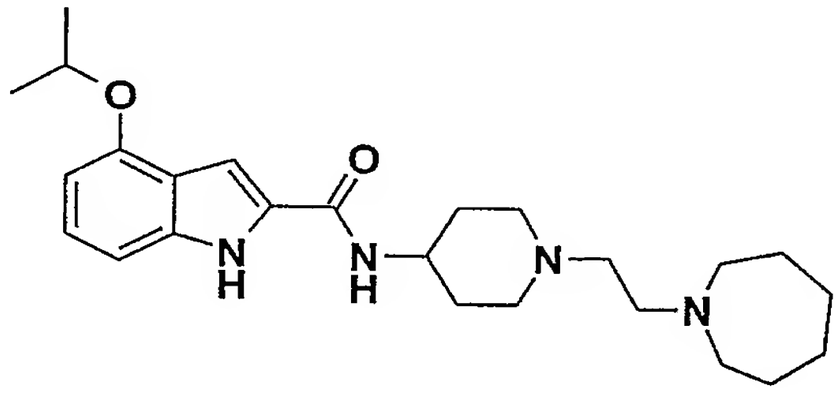
1. 4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



The methoxy derivative (example **8**) from above (100 mg, 0.25 mmol) is dissolved in 5 ml of DCM. A solution of BBr3 (1M in DCM, 2.5 ml, 2.5 mmol) is added and the mixture is stirred for 18 hours. It is then poured onto ice and washed with EtOAc (30 ml). The pH of the water layer is adjusted to 9 and extracted twice with EtOAc. The organic layers are combined washed with brine, dried over anhydrous sodium sulfate and evaporated.
MS (ESI): 385.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 9.62 (s, 1H), 8.14 (d, 1H), 7.2 (d, 1H), 6.94 (t, 1H), 6.86 (d, 1H), 6.37 (d, 1H), 3.75 (m, 1H), 2.89 (m, 2H), 2.53-2.65 (m, 6H), 2.39 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.47-1.68 (m, 10H), 1.25 (m, 1H).

Example 10

1. 4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-isopropoxy-1H-indole-2-carboxylic acid **27** (preparation see below) and amine **6**.
MS (ESI): 427.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.24 (d, 1H), 7.22 (d, 1H), 7.06 (t, 1H), 6.98 (d, 1H), 6.51 (d, 1H), 4.75 (m, 1H), 3.75 (m, 1H), 2.99 (m, 2H), 2.53-2.64 (m, 6H), 2.39 (m, 2H), 2.02 (m, 2H), 1.77 (m, 2H), 1.49-1.63 (m, 10H), 1.35 (d, 6H).

Synthesis of 4-isopropoxy-1H-indole-2-carboxylic acid (27):

(1) Step A: 4-Hydroxy-1H-indole-2-carboxylic acid methyl ester (**28**)

To an ice cold solution of 4-methyloxy-1H-indole-2-carboxylic acid methyl ester (1 g, 4.87 mmol) in DCM (10 ml) is added BBr3 (1M in DCM, 4.9 ml, 4.9 mmol). It is stirred for 1 hour and another equivalent (4.9 ml) of BBr3 is added. After another hour, the mixture is poured on ice and the pH is adjusted to 7 with sodium bicarbonate. Extraction with DCM gives a yellow powder.
MS (ESI): 192.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.78 (br s, 1H), 9.73 (s, 1H), 7.21 (d, 1H), 7.05 (dd, 1H), 6.89 (d, 1H), 6.4 (d, 1H), 3.86 (s, 3H).

(2) Step B: 4-Isopropoxy-1H-indole-2-carboxylic acid methyl ester (**29**)

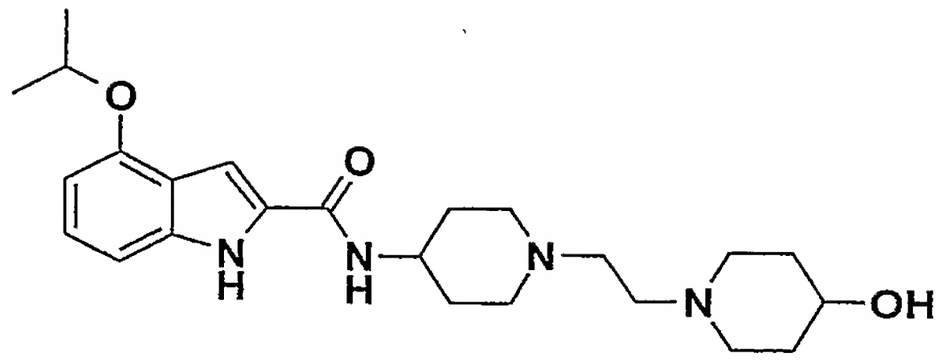
DEAD (0.227 ml, 1.47 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid methyl ester **28** (200 mg, 1.05 mmol), triphenylphosphine (384 mg, 1.47 mmol) and isopropanol (0.108 ml, 1.43 mmol) in 2 ml of THF. Stirring is continued for 20 minutes and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using cyclohexane/EtOAc (9/1).
MS (ESI): 234.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.89 (s, 1H), 7.26 (t, 1H), 7.07 (s, 1H), 6.98 (d, 1H), 6.54 (d, 1H), 4.72 (m, 1H), 3.85 (s, 3H), 1.33 (d, 6H).

(3) Step C: 4-Isopropoxy-1H-indole-2-carboxylic acid (**27**)

4-Isopropoxy-1H-indole-2-carboxylic acid methyl ester **29** (114 mg, 0.49 mmol) is dissolved in 5 ml of THF. A 2M-solution of LiOH in water (2.5 ml, 5 mmol) is added and the mixture is stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and EtOAc. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow powder.
MS (ESI): 219.9 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 7.14 (dd, 1H), 7.0 (m, 2H), 6.55 (d, 1H), 4.72 (m, 1H), 1.33 (d, 6H).

Example 11

1. 4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

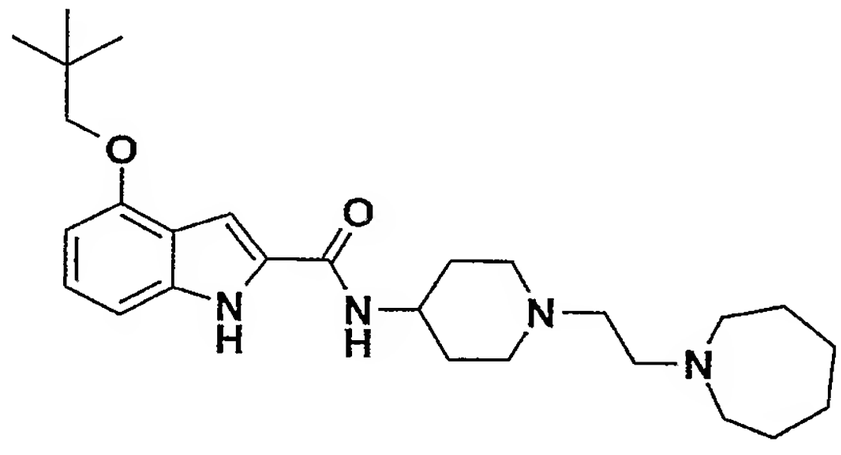


This compound is synthesized analogously to example 1 from 4-isopropoxy-1H-indole-2-carboxylic acid **27** (preparation see Example 10) and amine **9.**

MS (ESI): 429.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.2 (d, 1H), 7.19 (s, 1H), 7.02 (t, 1H), 6.94 (d, 1H), 6.48 (d, 1H), 4.72 (m, 1H), 4.5 (br. s, 1H), 3.74 (m, 1H), 3.25-3.45 (m, 3H), 2.86 (m, 2H), 2.71 (m, 2H), 2.37 (br. s, 4H), 2.0 (m, 4H), 1.73 (m, 4H), 1.54 (m, 2H), 1.33 (d, 6H).

Example 12

1. 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(2,2-dimethyl-propoxy)-1H-indole-2-carboxylic acid **30** (preparation see below) and amine **6.**

MS (ESI): 455.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.25 (d, 1H), 7.25 (d, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 3.72-3.84 (m, 3H), 2.92 (m, 1H), 2.54-2.63 (m, 6H), 2.41 (m, 2H), 2.04 (m, 2H), 1.79 (m, 2H), 1.5-1.65 (m, 11H), 1.1 (s, 9H).

Synthesis of 4-(2,2-dimethyl-propoxy)-1H-indole-2-carboxylic acid (30):

(1) Step A: 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid methyl ester (**31**)

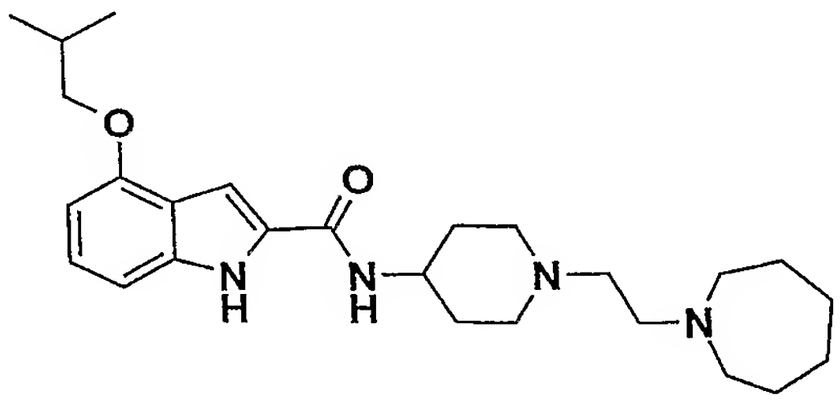
DEAD (0.414 ml, 2.66 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid methyl ester **28** (363 mg, 1.9 mmol), triphenylphosphine (698 mg, 2.66 mmol) and 2,2-dimethyl-propan-1-ol (228 mg, 2.58 mmol) in 8 ml of THF. Stirring is continued for 20 hours and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using cyclohexane/EtOAc (9/1).
MS (ESI): 261.9 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.39 (s, 1H), 7.23 (dd, 1H), 7.0 (d, 1H), 6.47 (d, 1H), 3.95 (s, 3H), 3.74 (s, 2H), 1.0 (s, 9H).

(2) Step B: 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (**30**)

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid methyl ester **31** (270 mg, 1.03 mmol) is dissolved in 20 ml of THF. A 2M-solution of LiOH in water (5.2 ml, 11 mmol) is added and the mixture is stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow powder.
MS (ESI): 248.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (br s, 1H), 7.13 (dd, 1H), 7.08 (s, 1H), 7.0 (d, 1H), 6.49 (d, 1H), 4.74 (s, 2H), 1.07 (s, 9H).

Example 13

1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see below) and amine **6**.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.99 (m, 1H), 2.53-

2.67 (m, 6H), 2.41 (m, 2H), 2.1 (m, 1H), 2.02 (m, 2H) 1.78 (m, 2H), 1.48-1.62 (m, 8H), 1.06 (d, 6H).

Synthesis of 4-isobutoxy-1H-indole-2-carboxylic acid (32):

(1) Step A: 4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (**33**)

To a solution of 4-benzyloxy-1H-indole-2-carboxylic acid ethyl ester (29 g, 98.2 mmol) in a mixture of MeOH (750 ml) and DCM (500 ml) is added 1 g of Pd/C (10%). It is hydrogenated under normal pressure for 24 hours. After filtration and evaporation a white powder is obtained.

MS (ESI): 206.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 9.69 (s, 1H), 7.2 (s, 1H), 7.05 (t, 1H), 6.98 (d, 1H), 6.38 (d, 1H), 4.33 (q, 2H), 1.32 (t, 3H).

(2) Step B: 4-Isobutoxy-1H-indole-2-carboxylic acid ethyl ester (**34**)

DEAD (10.2 ml, 65.28 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (9.57 g, 46.63 mmol), triphenylphosphine (17.12 g, 65.28 mmol) and isobutanol (5.9 ml, 63.42 mmol) in 100 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 3 hours and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using first cyclohexane as eluent, then increasing amounts of EtOAc (from 5% to 50%).

MS (ESI): 260.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.86 (s, 1H), 7.36 (s, 1H), 7.22 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 4.4 (q, 2H), 3.86 (d, 2H), 2.2 (m, 1H), 1.42 (t, 3H), 1.09 (d, 6H).

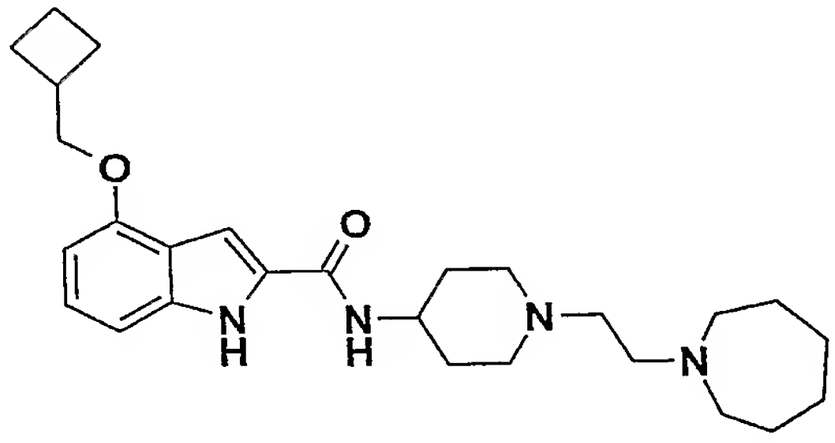
(3) Step C: 4-Isobutoxy-1H-indole-2-carboxylic acid (**32**)

4-Isobutoxy-1H-indole-2-carboxylic acid ethyl ester **34** (5.2 g, 19.9 mmol) is mixed with a 1M-solution of KOH in EtOH (99.5 ml, 99.5 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a beige powder.

MS (ESI): 234.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.74 (br s, 1H), 7.13 (dd, 1H), 7.06 (s, 1H), 7.0 (d, 1H), 6.49 (d, 1H), 3.85 (d, 2H), 3.35 (br s, 1H), 2.1 (m, 1H), 1.03 (d, 6H).

Example 14

1. 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid **35** (preparation see below) and amine **6**.
MS (ESI): 453.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.05 (d, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.78 (m, 1H), 2.55-2.7 (m, 6H), 2.4 (m, 2H), 1.83-2.18 (m, 8H), 1.76 (m, 2H) 1.47-1.63 (m, 10H).

Synthesis of 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid (35):

(1) Step A: 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid (**36**)

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and cyclobutyl-methanol (1.25 ml, 12.26 mmol) in 20 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5).
MS (ESI): 274.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.83 (s, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98 (d, 1H), 6.49 (d, 1H), 4.4 (q, 2H), 4.07 (d, 2H), 2.85 (m, 1H), 2.17 (m, 2H), 1.95 (m, 4H), 1.42 (t, 3H).

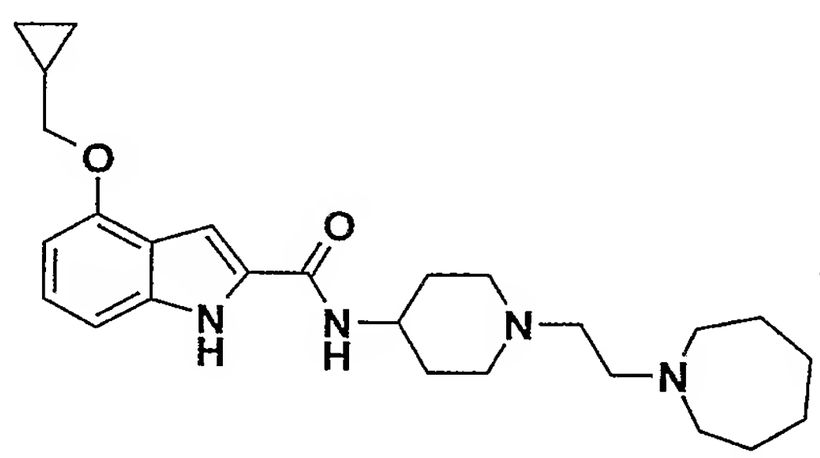
(2) Step B: 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid (**35**)

The 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid ethyl ester **36** obtained above is mixed with a 2M-solution of KOH in EtOH (16.9 ml, 33.8 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and DCM. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

MS (ESI): 246.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 11.74 (br. s, 1H), 7.14 (t, 1H), 7.03 (s, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.05 (d, 2H), 2.8 (m, 1H), 2.11 (m, 2H), 1.93 (m, 4H).

Example 15

1. 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-cyclopropylmethoxy-1H-indole-2-carboxylic acid **37** (preparation see below) and amine **6**.

MS (ESI): 439.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 3.9 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.76 (m, 2H) 1.47-1.63 (m, 10H), 1.3 (m, 1H), 0.61 (m, 2H), 0.37 (m, 2H).

Synthesis of 4-cyclopropylmethoxy-1H-indole-2-carboxylic acid (37):

(1) Step A: 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid (**38**)

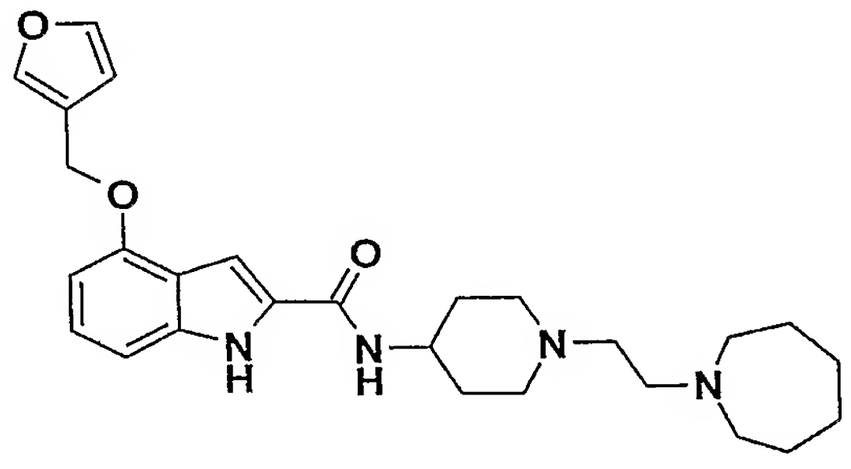
DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and cyclopropyl-methanol (1.05 ml, 12.26 mmol) in 20 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5).
MS (ESI): 260.1 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.85 (s, 1H), 7.4 (s, 1H), 7.19 (t, 1H), 6.99 (d, 1H), 6.45 (d, 1H), 4.4 (q, 2H), 3.95 (d, 2H), 1.41 (t, 3H), 1.34 (m, 1H), 0.66 (m, 2H), 0.4 (m, 2H).

(2) Step B: 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid (**37**)

The 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid ethyl ester **38** obtained above is mixed with a 2M-solution of KOH in EtOH (16.9 ml, 33.8 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and DCM. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.
MS (ESI): 232.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.84 (s, 1H), 7.55 (s, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.48 (d, 1H), 3.97 (d, 2H), 1.36 (m, 1H), 0.66 (m, 2H), 0.41 (m, 2H).

Example 16

1. 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid **39** (preparation see below) and amine **6**.

MS (ESI): 465.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H) 1.45-1.62 (m, 10H).

Synthesis of 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid (39):

(1) Step A: 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester (**40**)

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and furan-3-yl-methanol (1.18 ml, 12.26 mmol) in 10 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is triturated with ether and the white precipitate is filtered off. It contained mainly product. The mother liquor is purified by chromatography (cyclohexane:EtOAc / 95:5) and combined with the first precipitate.

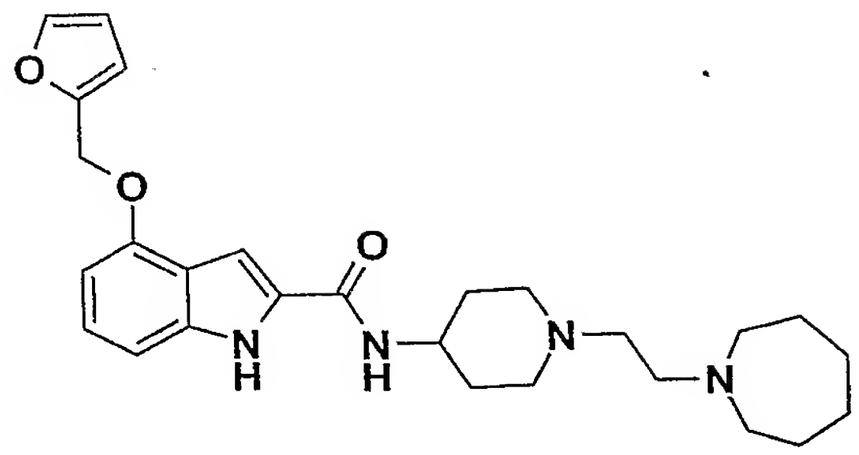
(2) Step B: 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid (**39**)

The 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester **40** obtained above is mixed with a 1M-solution of KOH in EtOH (35 ml, 35 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

MS (ESI): 258.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.71 (s, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.13 (m, 1H), 7.01 (m, 2H), 6.62 (m, 2H), 5.07 (s, 2H).

Example 17

1. 4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid **41** (preparation see below) and amine **6**.

MS (ESI): 465.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (d, 1H), 7.71 (s, 1H), 7.23 (s, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.63 (m, 2H), 6.48 (s, 1H), 5.13 (s, 2H), 3.72 (m, 1H), 2.86 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.74 (m, 2H) 1.45-1.6 (m, 10H).

Synthesis of 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid (41):

(1) Step A: 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester (**42**)

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and furan-2-yl-methanol (1.18 ml, 12.26 mmol) in 10 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5).

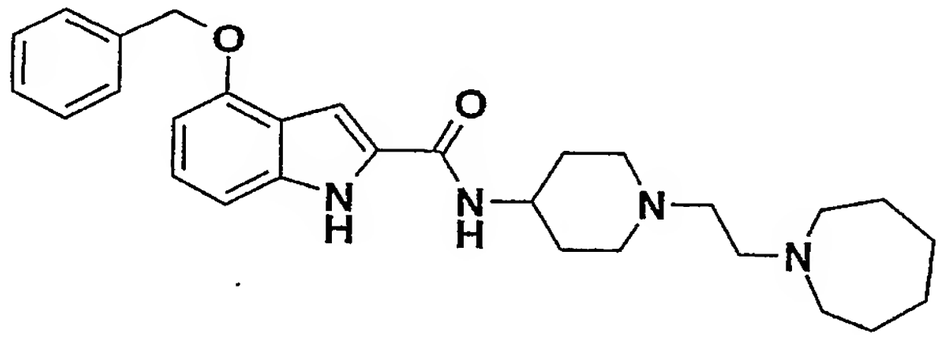
(2) Step B: 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid (**41**)

The 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester **42** obtained above is mixed with a 1M-solution of KOH in EtOH (13.3 ml, 13.3 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

1H-NMR (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.73 (s, 1H), 7.69 (s, 1H), 7.14 (t, 1H), 7.02 (d, 1H), 6.98 (s, 1H), 6.68 (d, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 5.16 (s, 2H).

Example 18

1. 4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

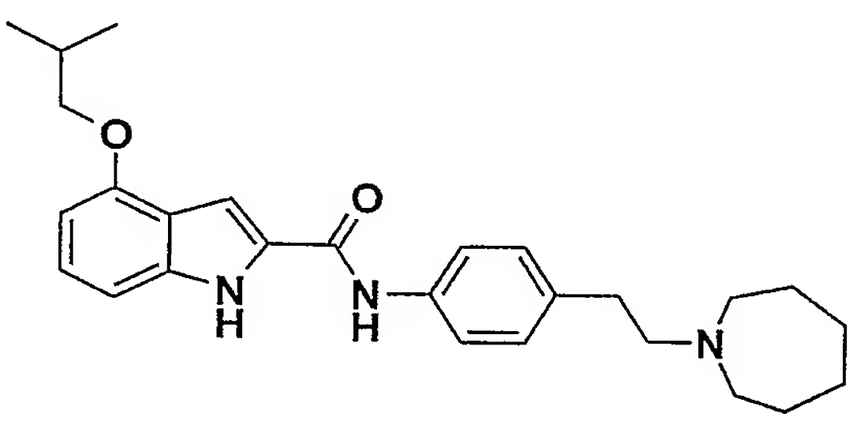


This compound is synthesized analogously to example 1 from 4-benzyloxy-1H-indole-2-carboxylic acid and amine **6**.

MS (ESI): 475.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.16 (d, 1H), 7.3-7.54 (m, 5H), 7.26 (d, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.6 (d, 1H), 5.18 (s, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.47-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.45-1.64 (m, 10H).

Example 19

1. 4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide

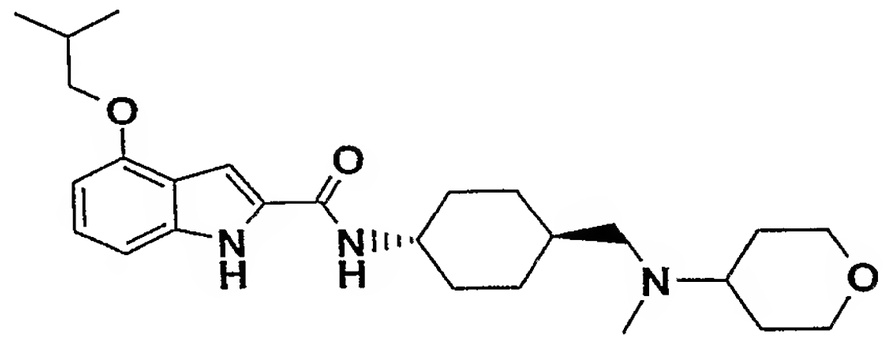


This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **26**.

MS (ESI): 434.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.07 (s, 1H), 7.67 (d, 2H), 7.48 (d, 1H), 7.18 (d, 2H), 7.08 (t, 1H), 7.01 (d, 1H), 6.49 (d, 1H), 3.88 (d, 2H), 2.57-2.62 (m, 8H), 2.13 (m, 2H), 1.48-1.63 (m, 8H), 1.08 (d, 6H).

Example 20

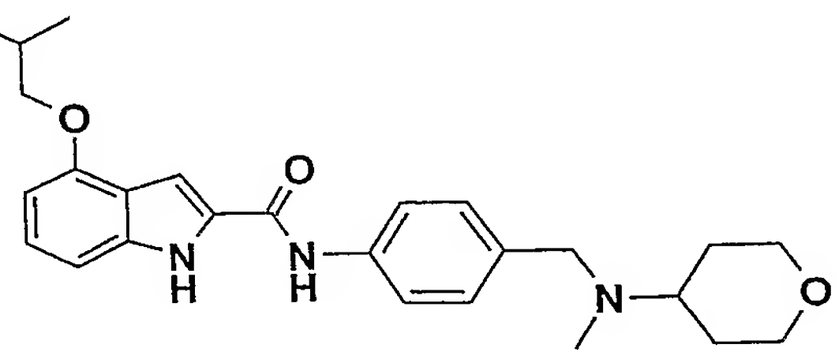
1. 4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-cyclohexyl)-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and trans-4-amino-cyclohexylmethyl)-methyl-(tetrahydro-pyran-4-yl)-amine (WO2000068203)
MS (ESI): 442.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.18 (d, 1H), 7.23 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.82-3.93 (m, 4H), 3.74 (m, 1H), 3.22-3.31 (m, 2H), 2.7 (s, 3H), 2.45 (m, 1H), 2.18 (m, 4H), 2.11 (m, 1H), 1.85 (m, 4H), 1.6 (m, 2H), 1.2-1.48 (m, 5H), 1.06 (d, 6H).

Example 21

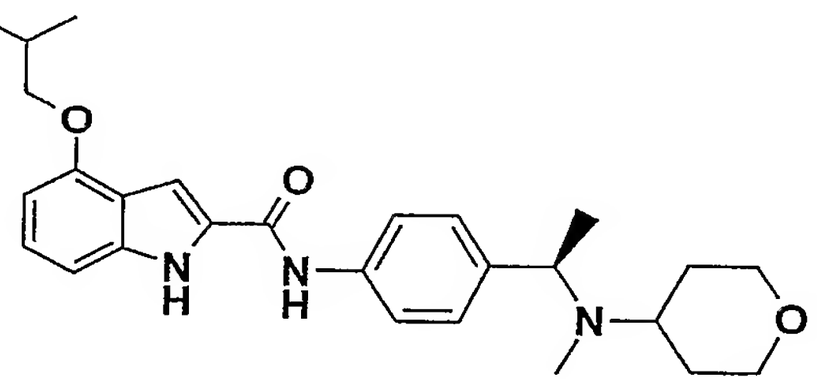
1. 4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine (WO9932468).
MS (ESI): 436.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.12 (s, 1H), 7.74 (d, 2H), 7.5 (s, 1H), 7.27 (d, 2H), 7.09 (t, 1H), 7.02 (d 1H), 6.5 (d, 1H), 3.84-3.94 (m, 4H), 3.52 (s, 2H), 3.22-3.32 (m, 2H), 2.6 (m, 1H), 2.08-2.2 (m, 4H), 1.72 (m, 2H), 1.53 (m, 2H), 1.07 (d, 6H).

Example 22

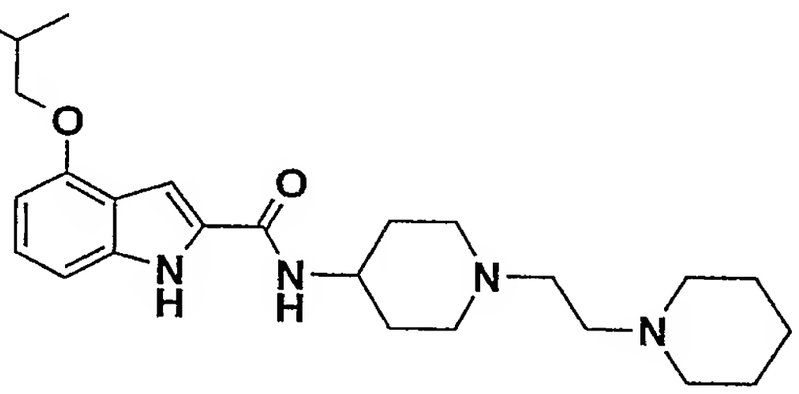
1. 4-Isobutoxy-1H-indole-2-carboxylic acid (4-{(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-phenyl)-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **17**.
MS (ESI): 450.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.66 (s, 1H), 10.12 (s, 1H), 7.73 (d, 2H), 7.5 (d, 1H), 7.3 (d, 2H), 7.09 (t, 1H), 7.02 (d, 1H), 6.5 (d, 1H), 3.76-3.91 (m, 5H), 3.1-3.33 (m, 2H), 2.68 (m, 1H), 2.04-2.2 (m, 4H), 1.36-1.68 (m, 4H), 1.28 (d, 3H), 1.08 (d, 6H).

Example 23

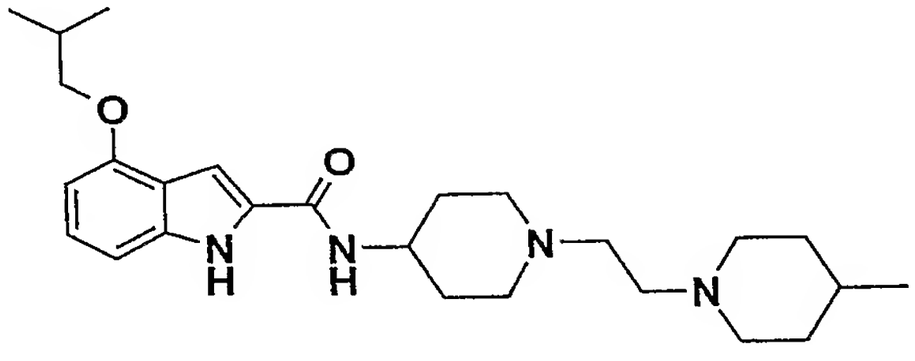
1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **4**.
MS (ESI): 427.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.88 (m, 2H), 2.38 (m, 8H), 2.1 (m, 1H), 2.02 (m, 2H), 1.78 (m, 2H), 1.32-1.63 (m, 9H), 1.07 (d, 6H).

Example 24

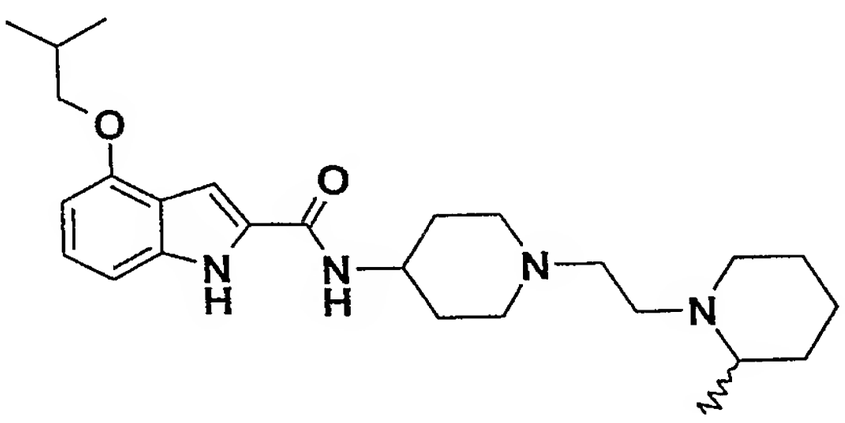
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **20**.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 3.86 (d, 2H), 3.75 (m, 1H), 2.86 (m, 4H), 2.4 (br s, 4H), 2.11 (m, 1H), 2.02 (m, 2H), 1.9 (m, 2H), 1.79 (m, 2H), 1.55 (m, 4H), 1.3 (m, 1H), 1.11 (m, 2H), 1.06 (d, 6H), 0.88 (d, 3H).

Example 25

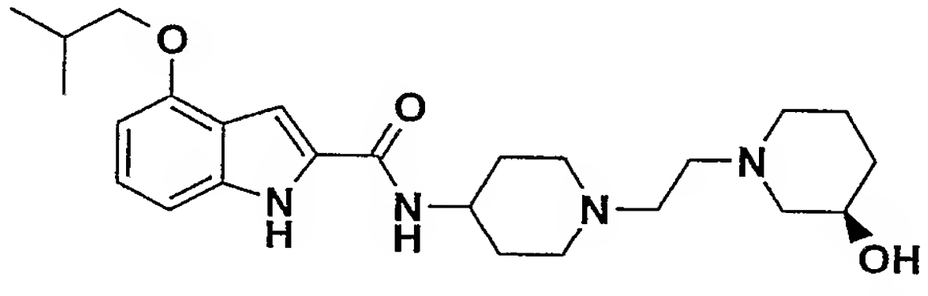
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **24.**
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.65-2.93 (m, 7H), 2.05-2.43 (m, 5H), 2.01 (m, 2H), 1.78 (m, 2H), 1.1-1.62 (m, 6H), 1.06 (d, 6H), 1.01 (d, 3H).

Example 26

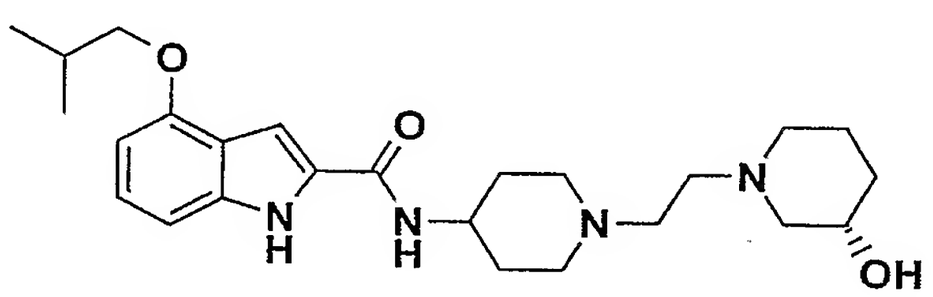
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **22.**
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (s, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.54 (d, 1H), 3.84 (d, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 2.62-2.93 (m, 2H), 2.49 (br s, 4H), 2.1 (m, 1H), 2.0 (m, 2H), 1.3-1.9 (m, 11H), 1.06 (d, 6H).

Example 27

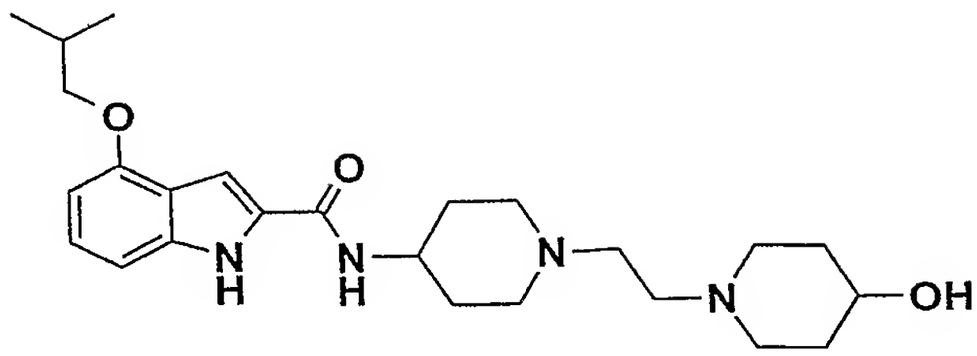
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is obtained by preparative separation of racemic material using a chiral HPLC stationary phase (CHIRALCEL OJ-H 1170). The absolute stereochemistry is assigned by comparison with the enantiomerically defined (R)-isomer (example 26).

Example 28

1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

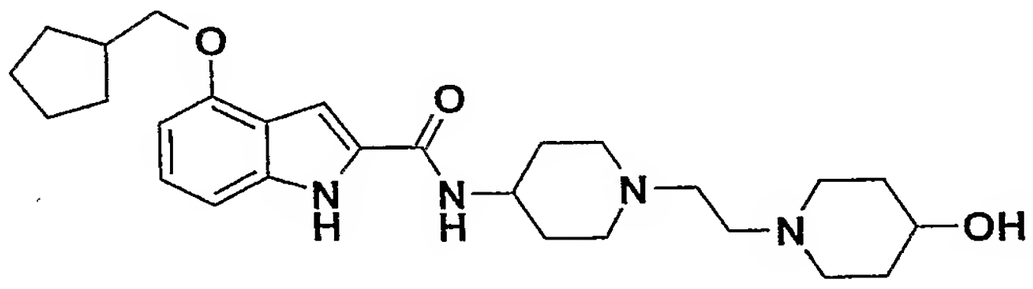


This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **9**.

MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Example 29

1. 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclopentylmethoxy-1H-indole-2-carboxylic acid **43** (preparation see below) and amine **9**.

MS (ESI): 469.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.19 (d, 1H), 7.18 (s, 1H), 7.01 (t, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.48 (br. s, 1H), 3.93 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 3.15 (br.s, 1H), 2.86 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H) 1.99 (m, 4H), 1.25-1.88 (m, 16H).

Synthesis of 4-cyclopentylmethoxy-1H-indole-2-carboxylic acid (43):

(1) Step A: 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid ethyl ester (**44**)

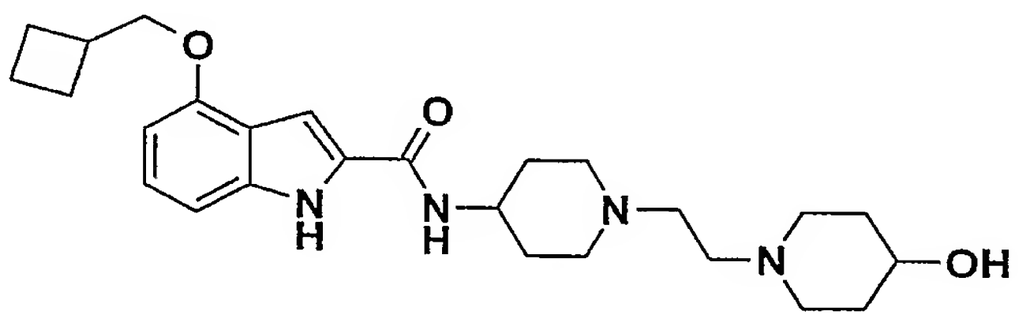
DEAD (5.3 ml, 34.1 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (2 g, 24.36 mmol), triphenylphosphine (8.95 g, 34.1 mmol) and cyclopentyl-methanol (3.58 ml, 33.13 mmol) in 30 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 90:10).
MS (ESI): 288.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.86 (br. s, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98 (d, 1H), 6.48 (d, 1H), 4.4 (q, 2H), 3.98 (d, 2H), 2.47 (m, 1H), 1.89 (m, 2H), 1.65 (m, 4H), 1.42 (t, 3H and overlapping m, 2H).

(2) Step B: 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid (**43**)

The 4-cyclopentylmethoxy-1H-indole-2-carboxylic acid ethyl ester **44** obtained above is mixed with a 2M-solution of KOH in EtOH (33.8 ml, 67.6 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.
MS (ESI): 260.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.73 (br. s, 1H), 7.12 (t, 1H), 7.02 (s, 1H), 6.98 (d, 1H), 6.5 (d, 1H), 3.96 (d, 2H), 2.39 (m, 1H), 1.82 (m, 2H), 1.6 (m, 4H), 1.4 (m, 2H).

Example 30

1. 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

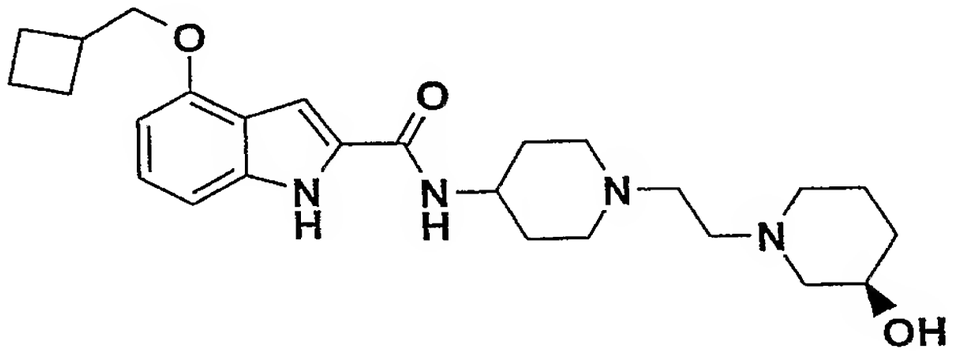


This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid **35** (preparation see Example 14) and amine **9**.
MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.49 (s, 1H), 4.05 (d, 2H), 3.73 (m, 1H), 3.41 (m,

1H), 2.87 (m, 2H), 2.78 (m, 1H), 2.7 (m, 2H), 2.38 (m, 4H) 2.14 (m, 2H), 1.83-2.07 (m, 8H), 1.76 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Example 31

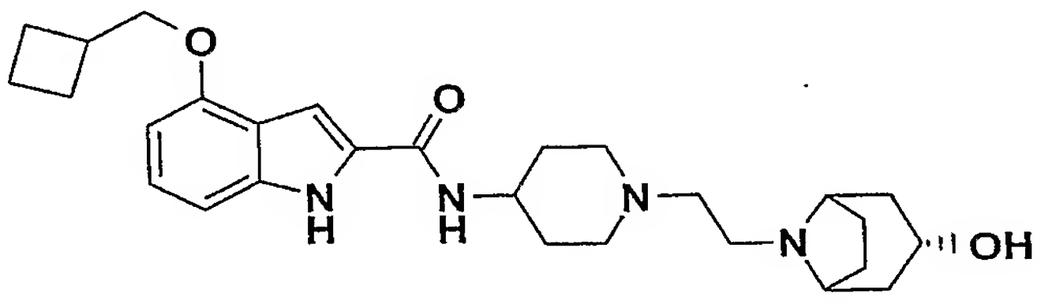
1. 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid **35** (preparation see example 14) and amine **22**.
MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.22 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.47 (d, 1H), 4.56 (br s, 1H), 4.05 (d, 2H), 3.75 (m, 1H), 3.43 (m, 1H), 2.88 (m, 3H), 2.78 (m, 1H), 2.68 (m, 1H), 2.42 (br. s, 4H), 1.83-2.2 (m, 8H), 1.77 (m, 4H), 1.56 (m, 4H), 1.38 (m, 2H).

Example 32

1. 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

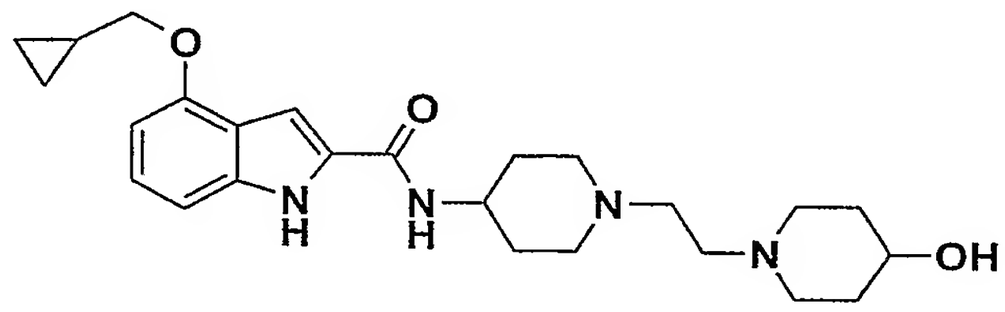


This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid **35** (preparation see example 14) and amine **12**.

MS (ESI): 481.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.31 (br s, 1H), 4.04 (d, 2H), 3.8 (br. S, 1H), 3.74 (m, 1H), 2.89 (m, 2H), 2.78 (m, 1H), 2.42 (br. m, 6H), 1.7-2.2 (m, 16H), 1.56 (m, 4H).

Example 33

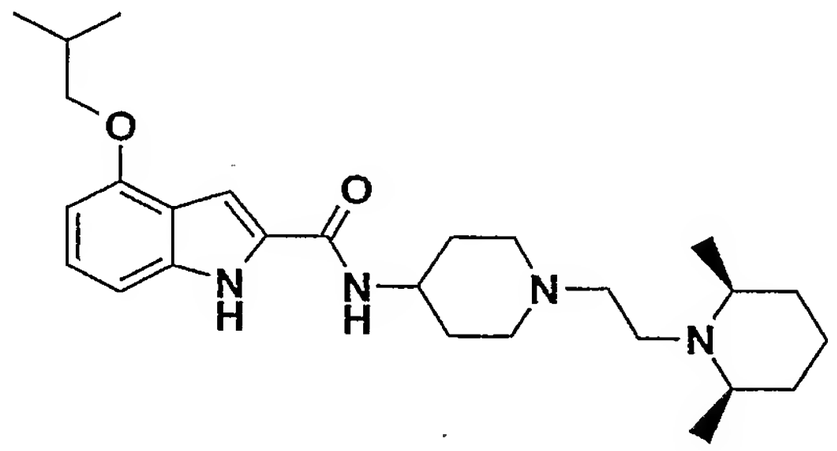
1. 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclopropylmethoxy-1H-indole-2-carboxylic acid **37** (preparation see example 15) and amine **9**.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 4.49 (d, 1H), 3.91 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 2.86 (m, 2H), 2.71 (m, 2H), 2.38 (br. s, 4H) 1.99 (m, 4H), 1.75 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.22-1.42 (m, 3H), 0.61 (m, 2H), 0.37 (m, 2H).

Example 34

1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

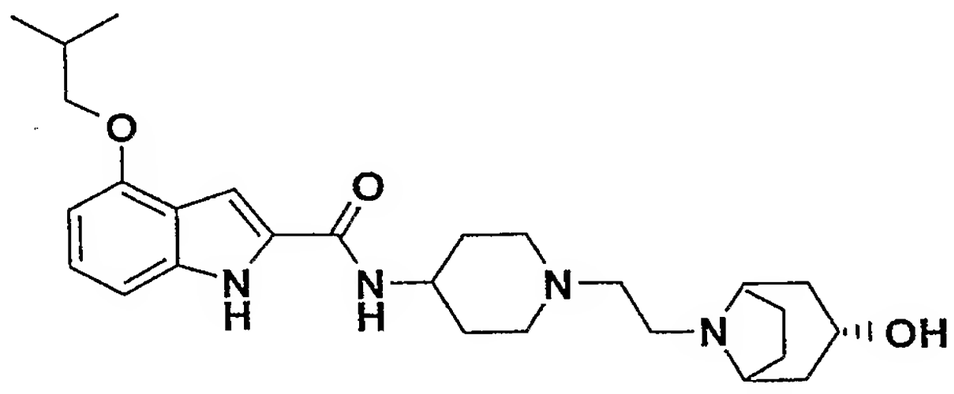


This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13) and amine **15**.

MS (ESI): 455.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.2 (d, 1H), 7.22 (d, 1H), 7.04 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.7 (m, 2H), 2.43 (m, 2H), 2.32 (m, 2H), 2.1 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.45-1.65 (m, 5H), 1.0-1.35 (m, 16H).

Example 35

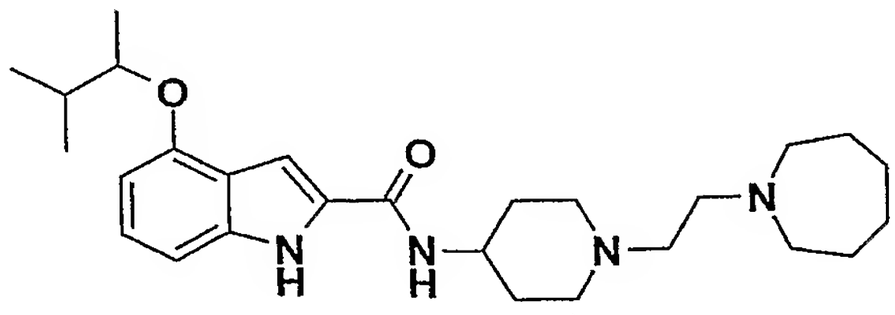
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see Example 13) and amine **12**.
MS (ESI): 469.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.23 (d, 1H), 7.72 (s, 1H), 6.9-7.1 (m, 2H), 6.46 (d, 1H), 4.57 (br s, 1H), 3.85 (d, 2H), 3.77 (m, 1H), 3.2-3.7 (br m, 4H), 2.94 (m, 2H), 2.75 (m, 2H), 2.56 (m, 2H), 1.5-2.25 (m, 15H), 1.06 (d, 6H).

Example 36

1. 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(1,2-dimethyl-propoxy)-1H-indole-2-carboxylic acid **45** (preparation see below) and amine **6**.

MS (ESI): 455.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 8.2 (d, 1H), 7.18 (d, 1H), 7.02 (dd, 1H), 6.93 (d, 1H), 6.47 (d, 1H), 4.37 (m, 1H), 3.74 (m, 1H), 2.88 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 1.89-2.06 (m, 3H), 1.75 (m, 2H), 1.46-1.62 (m, 10H), 1.24 (d, 3H), 1.0 (m, 6H).

Synthesis of 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (45):

(1) Step A: 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid ethyl ester (**46**)

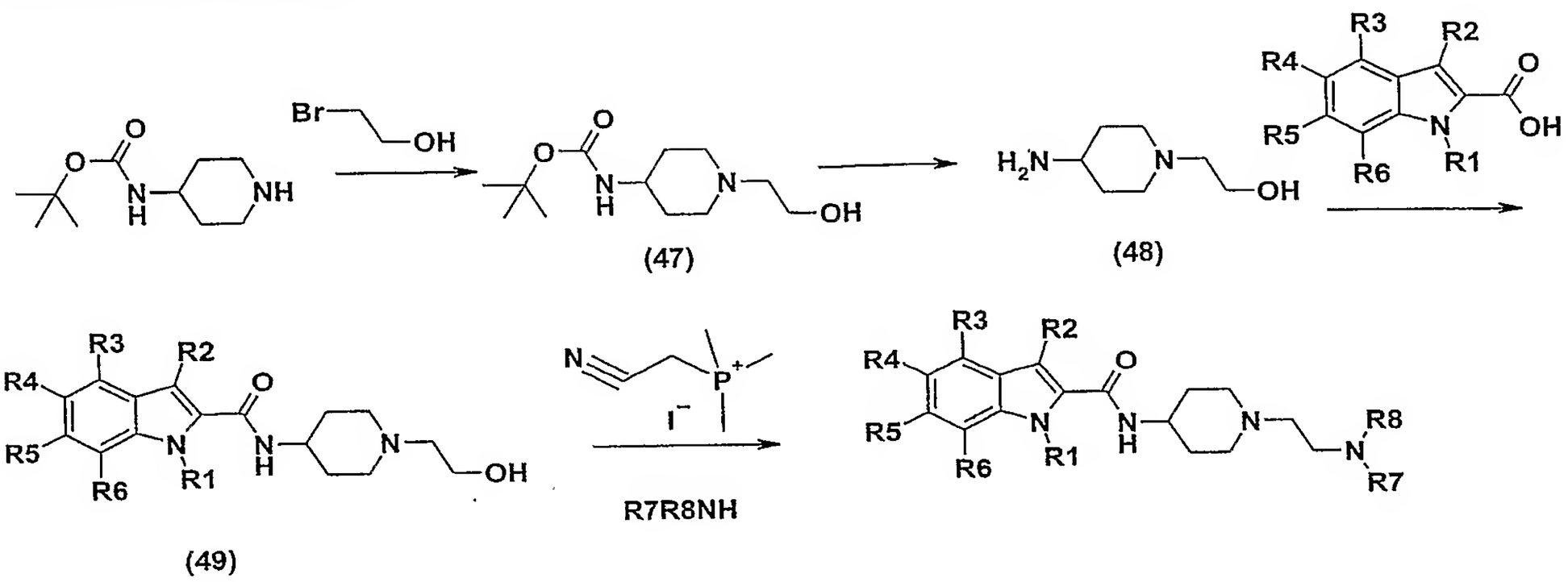
DEAD (5.3 ml, 34.1 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester **33** (5 g, 24.36 mmol), triphenylphosphine (8.95 g, 34.1 mmol) and 3-Methyl-butan-2-ol (3.58 ml, 33.13 mmol) in 50 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 3 days and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using first cyclohexane as eluent, then increasing amounts of EtOAc (from 5% to 50%).
MS (ESI): 276.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.35 (s, 1H), 7.2 (dd, 1H), 6.96 (d, 1H), 6.5 (d, 1H), 4.4 (q, 2H), 4.34 (t, 1H), 2.03 (m, 1H), 1.42 (t, 3H), 1.31 (d, 3H), 1.04 (m, 6H).

(2) Step B: 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (**45**)

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid ethyl ester **46** (2.4 g, 8.72 mmol) is mixed with a 1M-solution of KOH in EtOH (43.6 ml, 87.2 mmol) and stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a beige powder.
MS (ESI): 248.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.92 (br s, 1H), 7.52 (s, 1H), 7.27 (m, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.34 (m, 1H), 2.02 (m, 1H), 1.33 (d, 3H), 1.04 (m, 6H).

Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 6.

Reaction Scheme 6:



(49)

(1) [1-(2-Hydroxy-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (**47**)

Piperidin-4-yl-carbamic acid tert-butyl ester (5 g, 25 mmol) is dissolved in 100 ml of ethanol. After addition of sodium carbonate (10.6 g, 100 mmol), 2-bromo-ethanol (3.55 ml, 50 mmol) is added dropwise. The reaction mixture is refluxed for 16 h and then evaporated. The residue is dissolved in 100 ml of dichloromethane and filtrated. The residue is washed with DCM. The combined filtrates are evaporated, which afforded 10.1 g of a yellow oil, which is further purified by flash chromatography (silicagel, DCM / methanol / conc. ammonia 90:9:1) to give a white solid. MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(2) 2-(4-Amino-piperidin-1-yl)-ethanol (**48**)

Compound **47** (4.02 g, 16.46 mmol) are treated with 4M HCl in dioxane (60 ml, 240 mmol) and the mixture is stirred at room temperature for 1 h. The white precipitate is filtered off, washed with ether and dried under high vacuum. The mother liquor is concentrated and treatred with ether. The white solid is filtered off and dried under high vacuum.
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m,

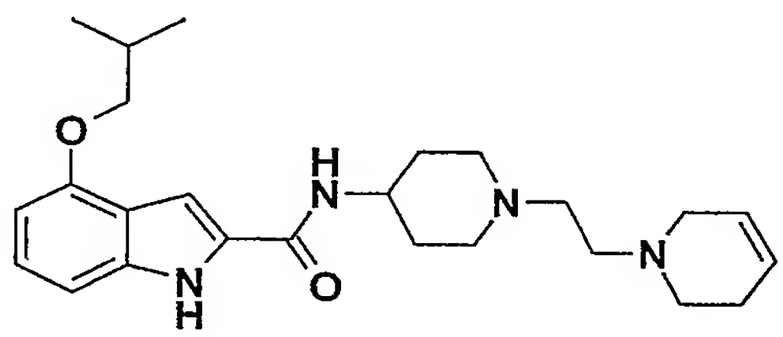
1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(3) 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide (**49**)

4-Isobutoxy-1H-indole-2-carboxylic acid **32** (preparation see example 13, 1 g, 4.29 mmol) is suspensed in 5ml of DMF, cooled to 0°C and treated with Hünig's Base (1.46 ml, 8.58 mmol). The mixture is stirred for 15 min at 0°C. In a separate reaction flask, compound **48** (931 mg, 4.29 mmol) in 10 ml of DMF is cooled to 0°C, treated with 10M aqueous sodium hydroxide solution (0.858 ml, 8.58 mmol) and stirred for 15 min at this temperature. This solution is added to the above mentioned mixture, followed by benzotriazol-1-yl-oxytripyrrolidinphosphonium hexafluorophosphate (PyBOP, 2.34 g, 4.5 mmol) and is stirred for 4 h at room temperature. The reaction mixture is diluted with ethyl acetate and washed with 2N sodium hydroxide solution, water and brine. Evaporation gives a semisolid, yellow crude product, which is treated with ether, filtered of and washed with ether.
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Example 37

1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide

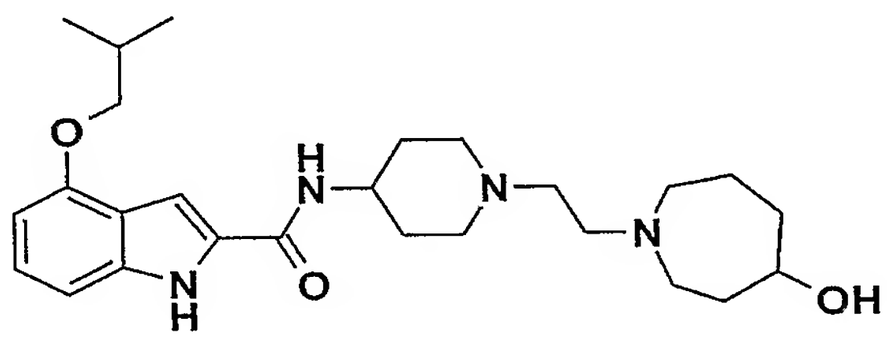


1,2,5,6-Tetrahydropyridine (25.4 µl, 0.279 mmol), cyanomethyl-triphenyl phosphonium iodide (162.5 mg, 0.6686 mmol) and Hünig's base (171 µl, 1 mmol) are added subsequently to a suspension of **49** (100 mg, 0.279 mmol) in 4 ml of propionitril. The mixture is stirred for 2h at 100°C, then diluted with ethyl acetate, washed with 1N sodium hydroxide solution and brine

and dried over sodium sulfate. Evaporation gives 138 mg of crude product, which is further purified by preparative HPLC (RP, acetonitrile / water).
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Example 38

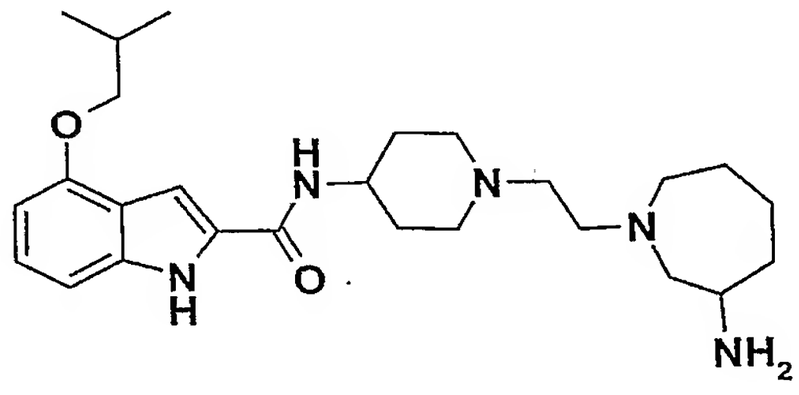
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 37 from 4-isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide **49** and azepan-4-ol.
MS (ESI): 457 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.19(d, 1H), 7.23 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 4.35 (d, 1H), 3.84 (d, 2H) 3.80-3.62 (m, 2H), 3.29 (s, 1H), 2.88 (d, 2H), 2.68-2.30 (m, 8H), , 2.14-2.06 (m, 1H), 2.0 (t, 2H), 1.83-1.34 (m, 9H), , 1.05 (d, 6H).

Example 39

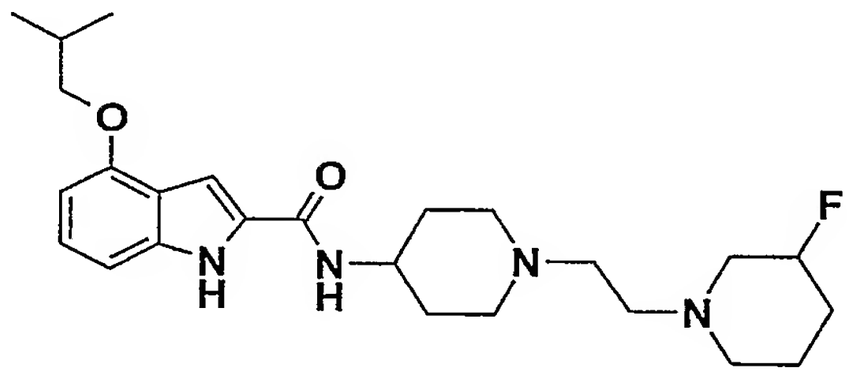
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 37 from 4-isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide **49** and azepan-3-ylamine.
MS (ESI): 456.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5(s, 1H), 8.27 (d, 1H), 7.24 (s, 1H), 7.05 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.80-3.70 (m, 1H), 2.89(m, 2H), 2.79 (m, 1H), 2.68-2.62 (m,1H), 2.60-2.52 (m,4H), 2.43-2.27 (m, 3H), 2.15-2.05 (m, 1H), 2.05-1.95 (m, 2H), 1.78-1.72 (m, 2H), 1.70-1.68 (m, 2H), 1.60-1.50 (m, 6H), 1.43-1.35 (m, 1H), 1.32-1.22 (m,1H), 1.05 (d, 6H).

Example 40

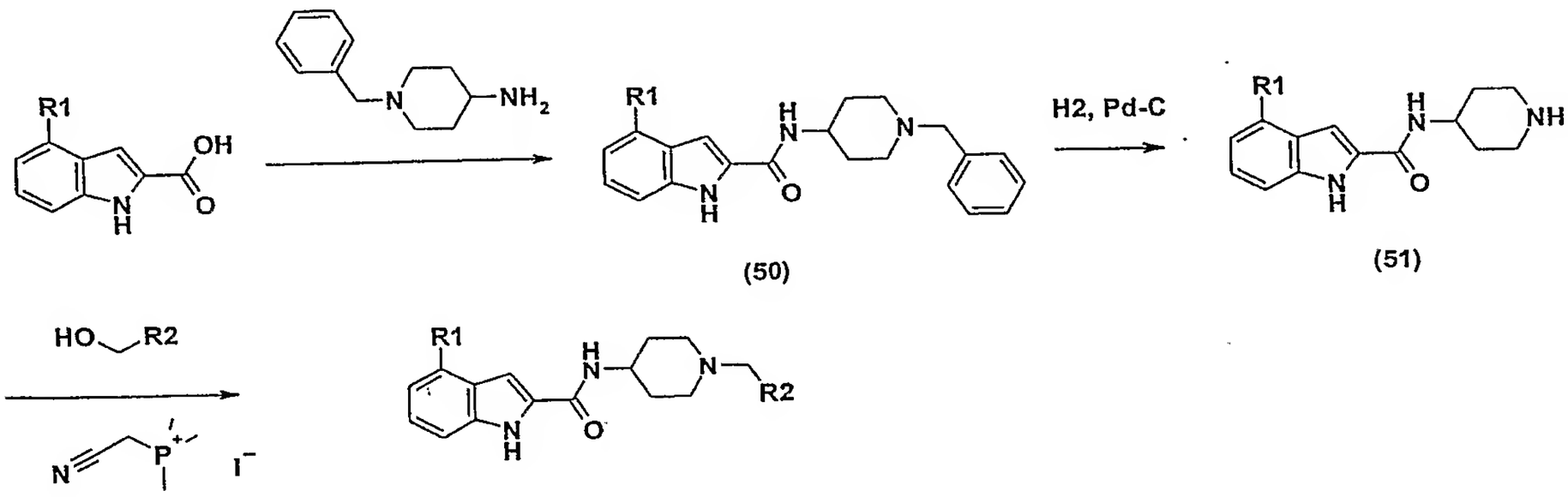
1. 4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



To a suspension of **49** (100 mg, 0.28 mmol), 3-fluoropiperidine hydrochloride (43 mg, 0.208 mmol) and DIEA (0.189 ml, 1.12 mmol) in 0.5 ml of propionitrile is added cyanomethyl-triphenyl phosphonium iodide (81 mg, 0.336 mmol). The mixture is heated at 90°C for 14 hours. The resulting solution is then diluted with EtOAc (20 ml) and washed twice with saturated sodium bicarbonate, dried over sodium sulfate and evaporated. The crude product is further purified by preparative HPLC.
MS (ESI): 445.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 4.45-4.7 (m, 1H), 3.84 (d, 2H), 3.74 (m, 1H), 2.88 (m, 2H), 2.76 (m, 1H), 2.18-2.48 (m, 8H), 2.1 (m, 1H), 2.0 (m, 2H), 1.34-1.9 (m, 7H), 1.05 (d, 6H).

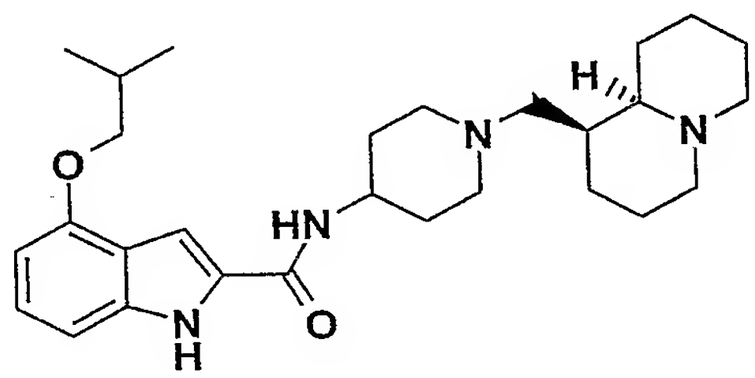
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 7.

Reaction Scheme 7:



Example 41

1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-((1*S*,9a*R*)-octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide

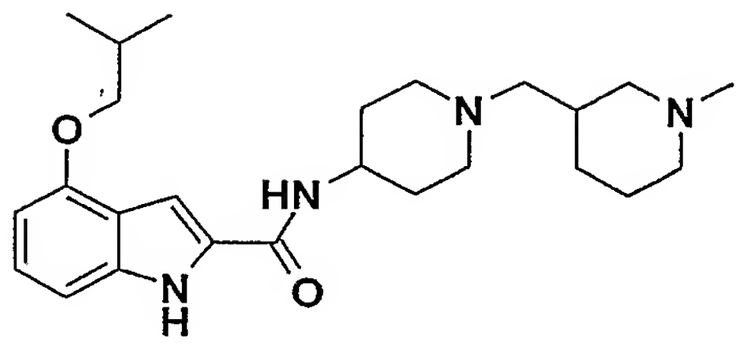


This compound is synthesized from the compound **51** (preparation see below) and octahydro-2H-chinolizin-1-ylmethanol analogously to the method described in example **37**.

MS (ESI): 467 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, NH), 8.16 (d, NH), 7.22(d, 1H), 7.02 (dd, 1H), 6.96(d, 1H) ,6,45(d, 1H), 3.83 (d, 2H), 3.75 (m,1H), 3.49(s,2H), 2.81(m, 2H), 2.70(m,2H), 2.29 (m, 1H), 2.15-2,00 (m, 2H),1,95-1,73 (m, 7H), 1.72-1.27 (m, 9H), 1.26-1,10(m, 2H), 1.05 (d, 6H).

Example **42**

1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-((3-*R,S*)-1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide



This compound is synthesized from the compound **51** (preparation see below) and (1-methyl-piperidin-3-yl)-methanol analogously to the method described in example **37.** MS (ESI): 427 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, NH), 8.18(d, NH), 7.21 (s, 1H), 7.02 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 3,85 (d, 2H), 3.75 (m, 1H), 2.88 (m, 1H), 2,78 (m, 2H), 2.62 (m, 1H), 2.12 (s, 3H), 2.13-2.05 (m,3H), 2.00-1.84 (m, 2H), 1.84-1.40 (m, 10H), 1.05 (d, 6H), 0.82 (m, 1H)

Synthesis of 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (51):

(1) Step A: 4-Isobutoxy-1H-indole-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (**50**)

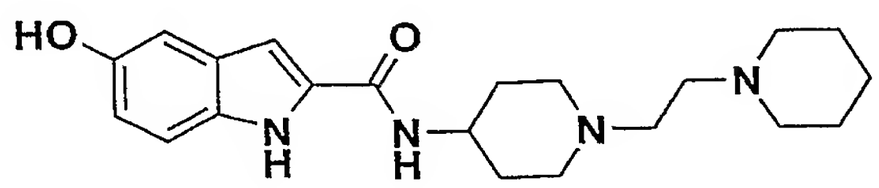
4-Isobutoxy-1H-indole-2-carboxylic acid **32** (4.7g, 20.1 mmol, preparation see example 13) and 1-benzyl-piperidin-4-ylamine (4.2 ml, 20.1 mmol) are dissolved in 70 ml of DMF and after addition of TBTU (7.3 g, 22.1 mmol) and ethyldiisopropylamine (13.8 ml, 80.4 mmol) the mixture is stirred at room temperature for 2 h. Then the solvent is evaporated at high vacuum. The residue is dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen arbonate and brine. The organic layers are dried over sodium sulfate and evaporated under reduced pressure to give a beige solid. MS (ESI): 406.5 $[M+H]^+$

(2) Step B: 4-Isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (**51**)

50 (8.1 g, 20 mmol) is dissolved in 200 ml of ethanol and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated to give a white solid. MS (ESI): 316 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.42 (d, 1H), 7.25 (s, 2H), 7.04 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.0 (m, 1H), 3.83 (d, 2H), 3.22 (m, 2H), 2.88 (m, 2H), 2.1 (m, 1H), 1.9 (m, 2H), 1.7 (m, 2H), 1.05 (d, 6H).

Example 43

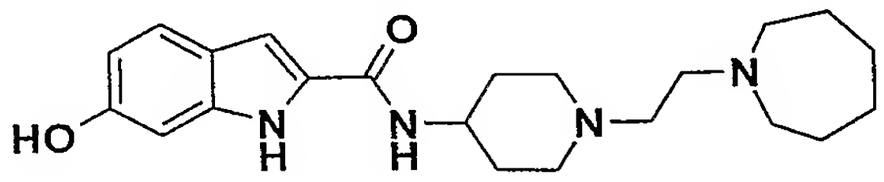
1. 5-Hydroxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



2.3 g of the product of example 2 and 230 mg of 10% palladium on charcoal in 70 ml of MeOH and 5 ml of DMF are stirred in a hydrogen atmosphere at room temperature under normal pressure for 4 hours. The suspension is diluted with DCM, filtered and the filtrate evaporated under reduced pressure. Drying at high vacuum and crystallization from ethyl acetate afforded off-white crystals, m.p. 225-226°C.
MS (ESI): 371.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.2 (s, 1H), 8.80 (br, 1H), 8.18 (d, 1H), 7.24 (d, 1H), 6.97 (s, 1H), 6.89 (bs, 1H), 6.72 (dd, 1H), 3.80 (m, 1H), 3.02 (m, 2H), 2.75 (m, 6H), 2.22 (m, 2H), 1.85 (m, 2h), 1.62 (m, 6H), 1.46 (m, 2H).

Example 44

1. 6-Hydroxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

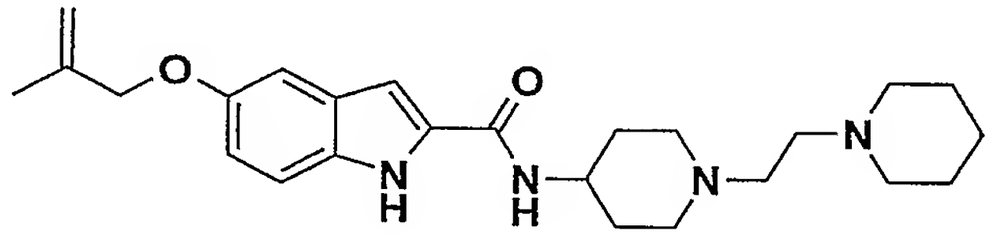


To a stirred solution of 917 mg of the product from example 4 in 46 ml of DCM under an argon atmosphere and cooled to ca. -70 °C (dry ice/acetone) are added 1.2 g of boron tribromide. The cooling bath is removed, the mixture stirred at room temperature for 18 hours and then poured into an ice-cold sat. aqueous sodium bicarbonate solution and stirred for 15 minutes. The mixture is evaporated under reduced pressure, the residue is taken up in EtOH, filtered, the insoluble residue rinsed with EtOH, and the yellow filtrate evaporated under reduced pressure. The residue is purified by chromatography (silica gel, DCM/MeOH/conc. ammonia, 80:18:2) to afford the product which is crystallized as yellow crystals from EtOH/Ether, m.p. 164 oC. MS (ESI): 385.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 9.12 (bs, 1H), 8.00 (d, 1H), 7.37 (d, 1H), 7.02 (bs, 1H), 6.78 (bs, 1H), 6.56 (dd, 1H),

3.75 (m, 1H), 2.83 9bd, 2H), 2.55 (br, 6H), 2.40 (br, 4H), 2.02 (m, 2H), 1.78 (m, 2H), 1.55 (m, 8H).

Example 45

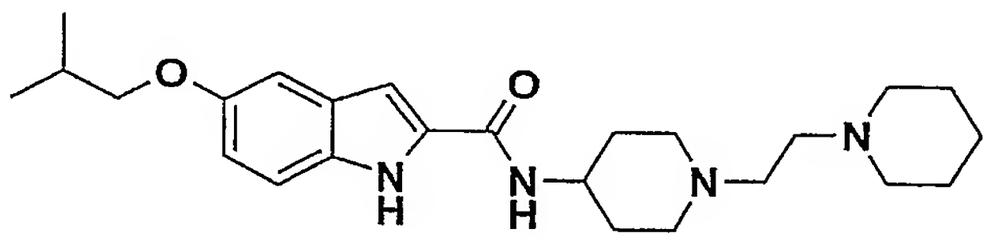
1. 5-(2-Methyl-allyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



278 mg of the product from example **43**, 125 mg of 3-bromo-2-methyl-1-propene, and 321 mg of cesium carbonate in 15 ml of DMF are stirred under an Argon atmosphere at 60°C for 8 hours. The reaction mixture is filtered, the filtrate evaporated under reduced pressure, and the residue dissolved in DCM. The DCM solution is washed twice with sat. aqueous potassium carbonate solution and with brine, the organic phases are dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue (208 mg) is purified by chromatography (Biotage, DCM/MeOH/conc. ammonia 95:4.5:0.5) and crystallization from ether/cyclohexane yielded colorless crystals, m.p. 211-212 oC. MS (ESI): 425.4 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.3 (s, NH), 8.16 (s, NH), 7.32 (d, 1H), 7.08 (dd, 2H), 6.88 (dd, 1H), 5.12 (s, 1H), 4.97 (bs, 1H), 4.48 (s, 2H), 3.79 (m, 1H), 2.90 (m, 2H), 2.50-2.30 (m, 7H), 2.03 (m, 2H), 1.80 (m, 4H), 1.60-1.30 (m, 10H).

Example 46

1. 5-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

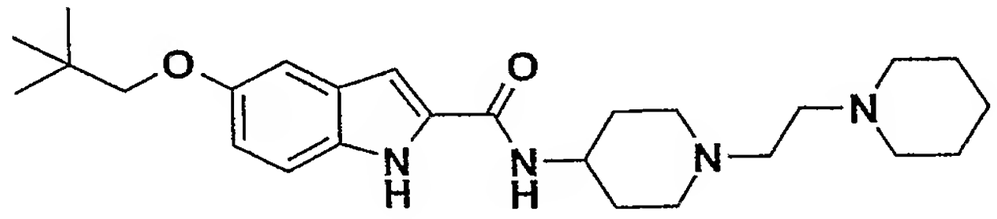


This compound is synthesized from the compound from example **43** and isobutyl bromide analogously to the method described in example **45**. MS (ESI): 427.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.17 (d, NH), 7.32 (d, 1H), 7.05 (dd, 2H), 6.83 (dd, 1H), 3.77 (m, 1H),

3.74 (d, 2H), 2.90 (m, 2H), 2.45-2.30 (m, 6H), 2.05 (m, 3H), 1.78 (m, 2H), 1.60-1.35 (m, 8H), 1.02 (d, 6H).

Example 47

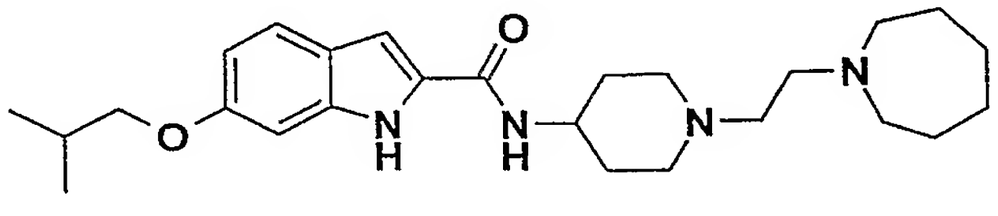
1. 5-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized from the compound from example **43** and 1-bromo-2,2-dimethyl-propane analogously to the method described in example **45**. MS (ESI): 441.4 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.3 (s, NH), 8.15 (d, NH), 7.30 (d, 1H), 7.03 (dd, 1H), 6.83 (dd, 1H), 3.75 (m, 1H), 3.61 (s, 2H), 2.88 (m, 2H), 2.37 (m, 8H), 2.01 (m, 2H), 1.78 (m, 2H), 1.60-1.40 (m, 7H), 1.35 (m, 2H), 1.02 (s, 9H).

Example 48

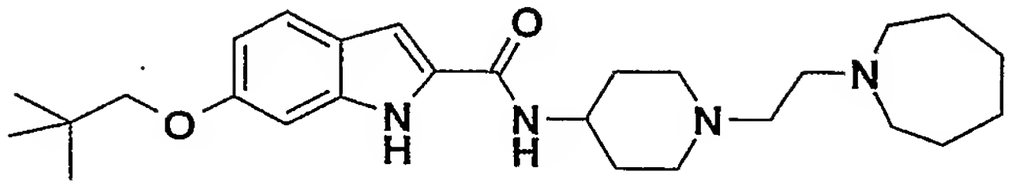
1. 6-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized from the compound from example **44** and isobutyl bromide analogously to the method described in example **45**. MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 9.05 (d, NH), 7.45 (d, 1H), 7.07 (s, 1H), 6.86 (bs, 1H), 6.70 (dd, 1H), 3.72 (m, 3H), 2.38 (m, 2H), 2.60-2.50 (m, 4H), 2.38 (m, 2H), 2.02 (m, 2H), 1.78 (m, 2H), 1.55 (m, 10 H), 1.00 (d, 6H).

Example 49

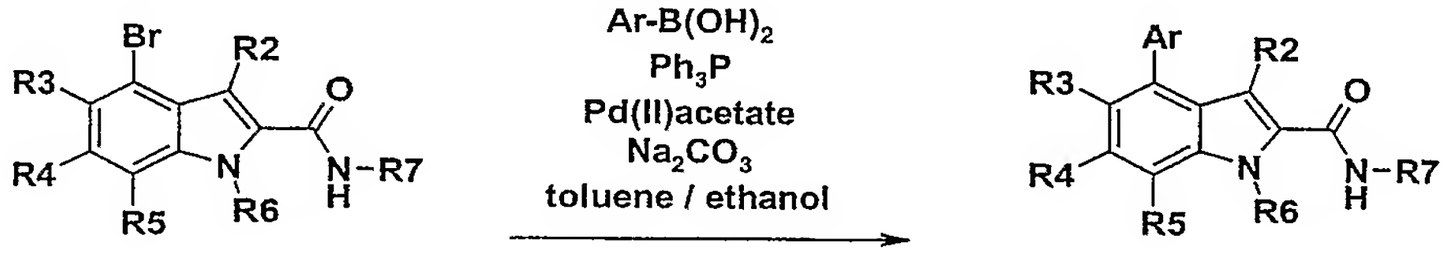
1. 6-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-azepann-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized from the compound from example **44** and 1-bromo-2,2-dimethyl-propane analogously to the method described in example **45**. MS (ESI): 455.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 8.08 (d, NH), 7.45 (d, 1H), 7.07 (bs, 1H), 6.85 (bs, 1H), 6.70 (dd, 1H), 3.75 (m, 1H), 3.61 (s, 2H), 2.89 (bd, 2H), 2.60-2.50 (m, 12H), 2.40 (m, 2H), 2.02 (m, 2H), 1.78 (m, 2H), 1.60-1.50 (m, 4H), 1.03 (s, 9H).

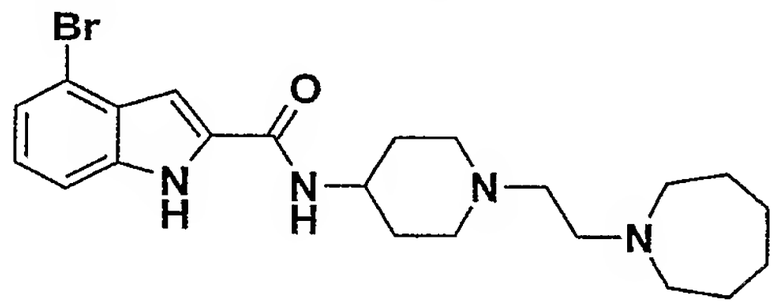
The 4-aryl-indole-2-carboxamides are generally prepared by a Suzuki coupling of the 4-bromo-indole-2-carboxamides with the corresponding aryl-boronic acids (Reaction Scheme 8).

Reaction Scheme 8:



(52), (53), (54), (55)

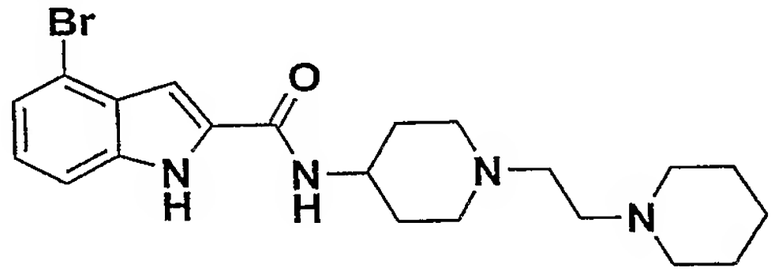
(1) 4-Bromo-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide (**52**)



4-Bromo-1H-indole-2-carboxylic acid (1.5 g, 3.1 mmol), 1-(2-azepan-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (**6**) (2.1 g, 3.1 mmol) and DIEA (4.3 ml, 12.4 mmol) are dissolved under argon atmosphere in DMF (25 ml). TBTU (2.3 g, 3.4 mmol) is added at room temperature. The reaction mixture is stirred for 2 h at r.t., evaporated under high vacuum, dissolved in ethyl acetate and washed twice with 5% aqueous NaHCO3 solution. The

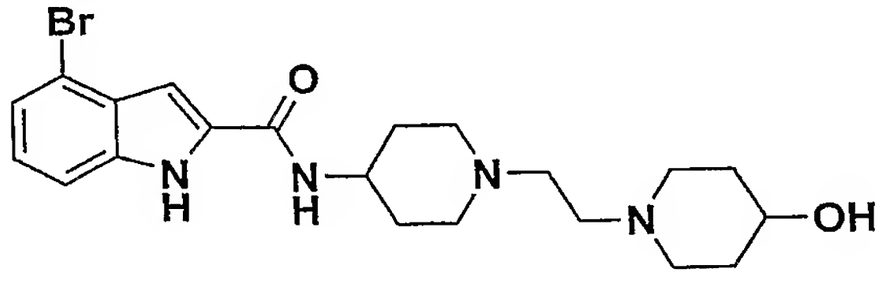
organic layers are dried over sodium sulfate. Evaporation under reduced pressure gives a beige solid.
MS (ESI): 447.1, 449.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.25 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.55-2.68 (m, 6H), 2.4 (m, 2H), 2.05 (m, 2H), 1.78 (m, 2H), 1.5-1.62 (m, 10H).

(2) 4-Bromo-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide (**53**)



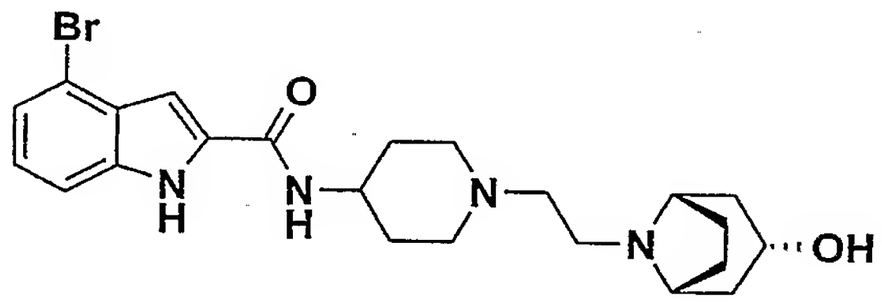
This compound is synthesized from 4-bromo-1H-indole-2-carboxylic acid and amine **4** analogous to the method described above for the synthesis of **52**.
MS (ESI): 433, 435 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.19 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.3-2.4 (m, 8H), 2.0 (m, 2H), 1.78 (m, 2H), 1.3-1.6 (m, 8H).

(3) 4-Bromo-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide (**54**)



This compound is synthesized from 4-Bromo-1H-indole-2-carboxylic acid and amine **9** analogous to the method described above for the synthesis of **52**.
MS (ESI): 449, 451.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.42 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.8 (m, 1H), 3.5 (m,1 H), 2.88 (m, 2H), 2.95 (m, 2H), 2.86 (m, 2H), 2.6 (m, 2H), 2.52 (m, 2H), 2.3 (m, 2H), 2.12 (m, 2H), 1.8 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H),1.43 (m, 2H).

(4) 4-Bromo-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide (**55**)

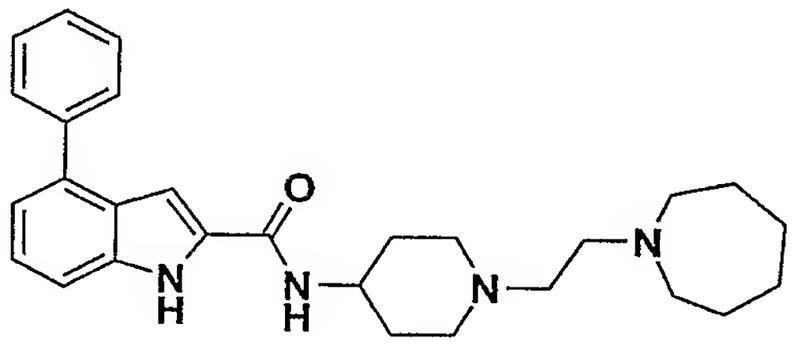


This compound is synthesized from 4-Bromo-1H-indole-2-carboxylic acid and amine **12** analogous to the method described above for the synthesis of **52**.

MS (ESI): 475.3, 477 $[M+H]^+$, 1H-NMR (DMSO-d_6, 150°C): δ (ppm) 11.7 (br s, 1H), 8.28 (br s, 1H), 7.49 (d, 1H), 7.25 (d, 1H), 7.15 (s, 1H), 7.1 (dd, 1H), 4.1 (br s, 1H), 3.97 (m, 3H), 3.5 (m,2 H), 3.0 (m, 2H), 2.5 (m, 6H), 1.9 – 2.2 (m, 10H).

Example 50

1. 4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

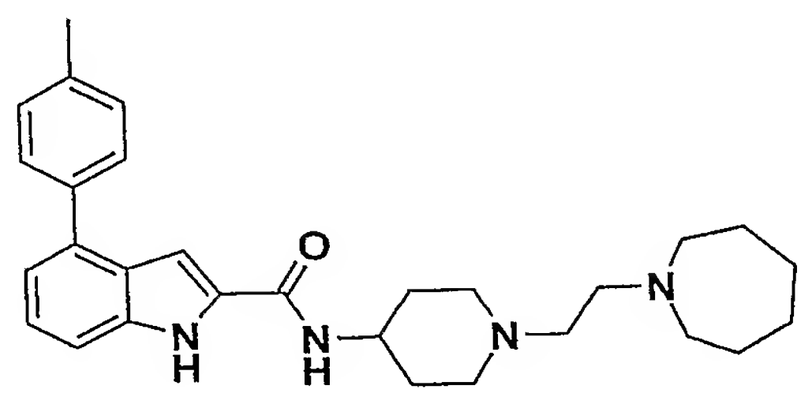


Bromindole (**52**, 150 mg, 0.335 mmol), phenyl-boronic acid (82 mg, 0.67 mmol) and triphenylphosphine (26.4 mg, 0.112 mmol) are dissolved in 10 ml of toluene. After addition of 1 ml of ethanol, argon is flushed through the mixture for 30 min. Then Pd(II)acetate (3 mg, 13.4 µmol) and 2M aqueous sodiumcarbonate (0.67 ml, 1.34 mmol) are added. The mixture is stirred under reflux for 3 h. After cooling down to r.t., the mixture is treated with 30 ml of ethyl acetate and 5 % aqueous NaHCO3 solution and filtrated over celite. The organic layer is separated and evaporation under reduced pressure gives 170 mg of crude product, which is further purified by flash chromatography (silica gel, ethyl acetate / methanol conc. NH3 90:10:2) and crystallization from ethyl acetate.

MS (ESI): 445.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.25 (d, 1H), 7.63 (d, 2H), 7.50 (dd, 2H), 7.40 (m, 2H), 7.31 (s, 1H), 7.23 (dd, 1H), 7.08 (d, 1H), 3.73 (m, 1H), 2.85 (m, 2H), 2.57 (m, 6H), 2.36 (m, 2H), 1.99 (m, 2H), 1.74 (m, 2H), 1.52 (m, 10H).

Example 51

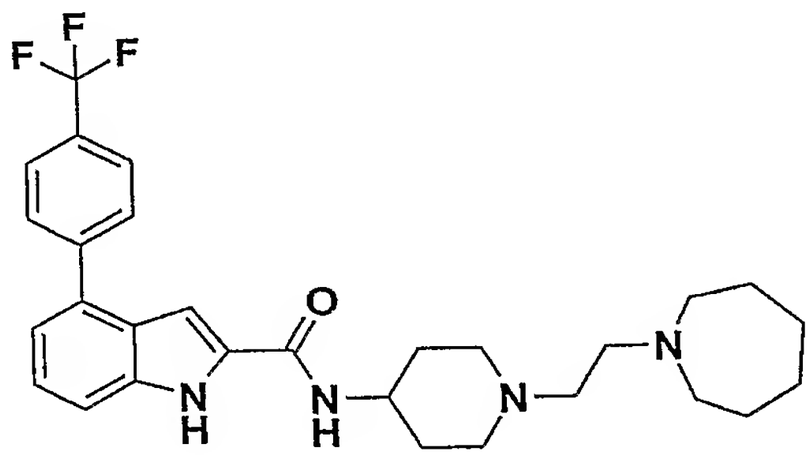
1. 4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and 4-p-tolyl boronic acid analogous to the method described in example **50**.
MS (ESI): 459 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.53 (d, 2H), 7.48 (d, 1H), 7.32 (d, 2H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 1H), 3.75 (m, 1H), 2.5-2.6 (m, 8H), 2.38 (s, 3H), 2.33-2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.55 (m, 10H).

Example 52

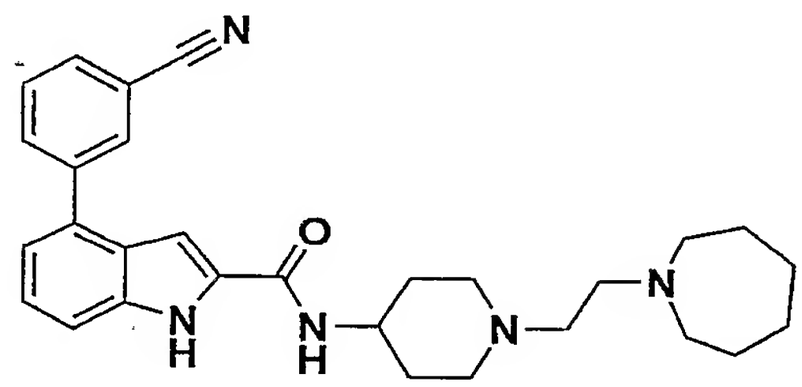
1. 4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and 4-trifluoromethyl-phenyl boronic acid analogous to the method described in example **50**.
MS (ESI): 513 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.25 (d, 1H), 7.85 (s, 4H), 7.48 (d, 1H), 7.32 (s, 1H), 7.28 (dd, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.78 (m, 2H), 1.48-1.55 (m, 10H).

Example 53

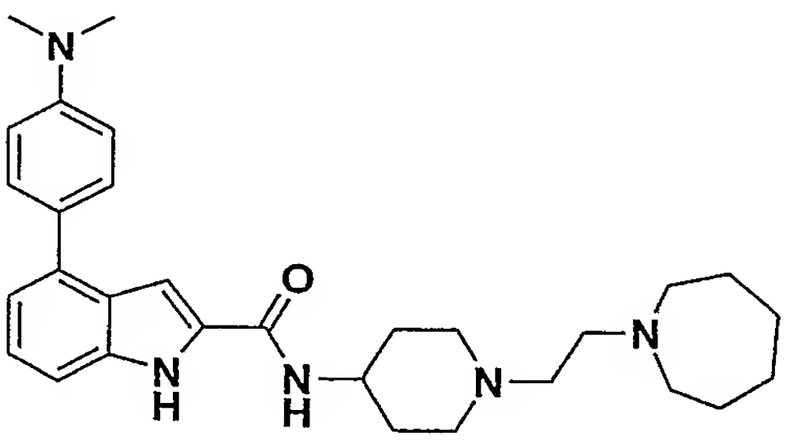
1. 4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and 3-cyano-phenyl boronic acid analogous to the method described in example **50**.
MS (ESI): 470.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.38 (d, 1H), 8.05 (s, 1H), 7.98 (dd, 1H), 7.88 (m, 1H), 7.72 (dd, 1H), 7.47 (d, 1H), 7.3 (d, 1H), 7.25 (d, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 54

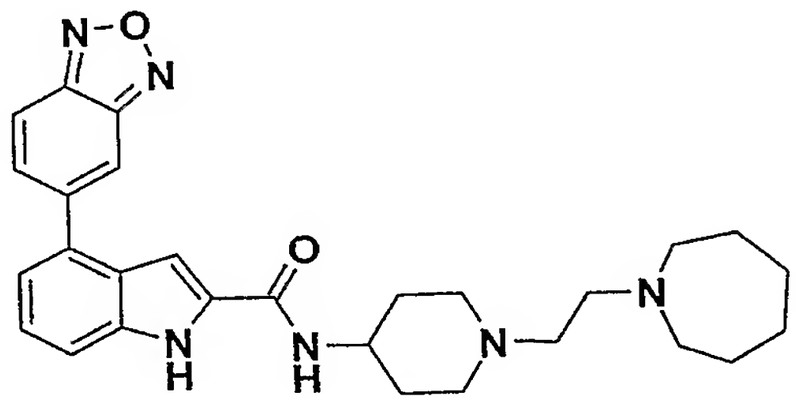
1. 4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and (4-dimethylamino-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 488.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 8.25 (d, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Example 55

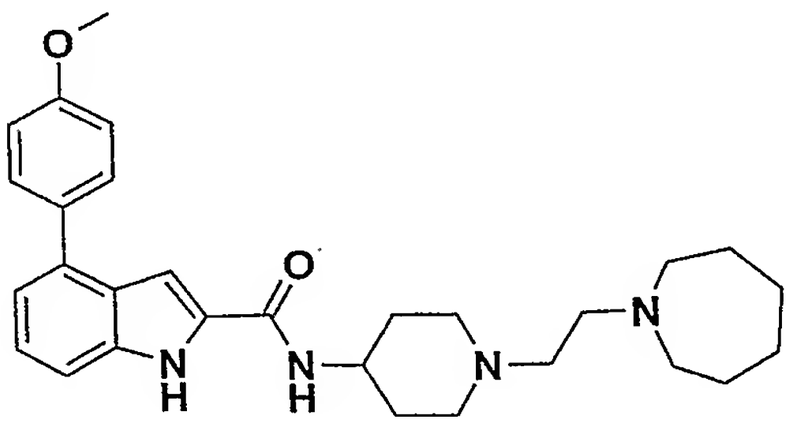
1. 4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and benzo[1,2,5]oxadiazol-5-yl-boronic acid analogous to the method described in example **50**.
MS (ESI): 487.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 8.18 (d, 1H), 7.95 (d, 1H), 7.52 (m, 1H), 7.38 (s, 1H), 7.3 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 56

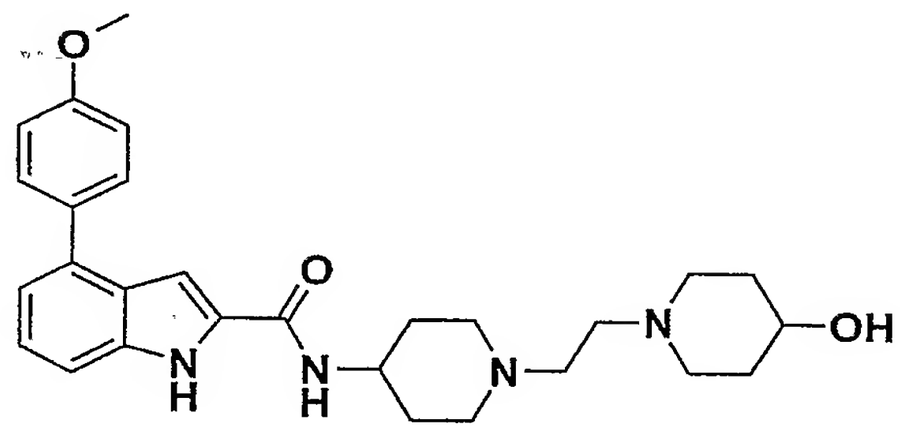
1. 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and (4-methoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 475.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.23 (d, 1H), 7.49 (d, 2H), 7.32 (m, 2H), 7.18 (dd, 1H), 7.0 (d, 1H), 6.85 (d, 2H), 3.75 (m, 1H), 2.97 (s, 6H), 2.87 (m, 2H), 2.56 (m, 6H), 2.48 (m, 2H), 2.0 (m, 2H), 1.77 (m, 2H), 1.52 (m, 10H).

Example 57

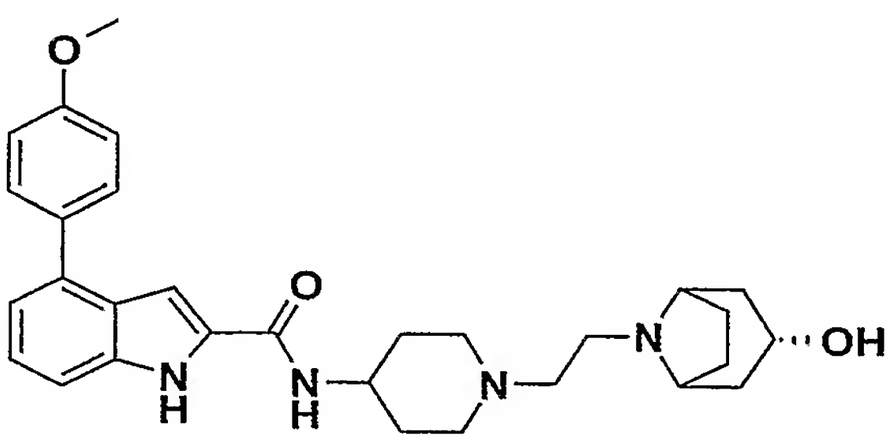
1. 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound **54** and (4-methoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 477.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.58 (d, 2H), 7.36 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.55 (br, 1H), 3.85 (s, 3H), 3.78 (m, 1H), 3.45 (m, 1H), 2.9 (m, 2H), 2.78 (m, 2H), 2.45 (m, 4H), 2.15 (m, 2H), 2.05 (m, 2H), 1.3 – 1.8 (m, 8H).

Example 58

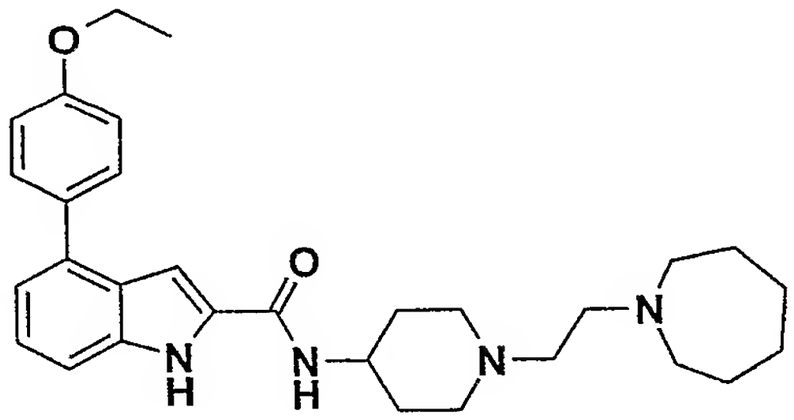
1. 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound **55** and (4-methoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 503.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (m, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.25 (br s, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.85 (m, 2H), 1.77 (m, 4H), 1.55(m, 4H).

Example 59

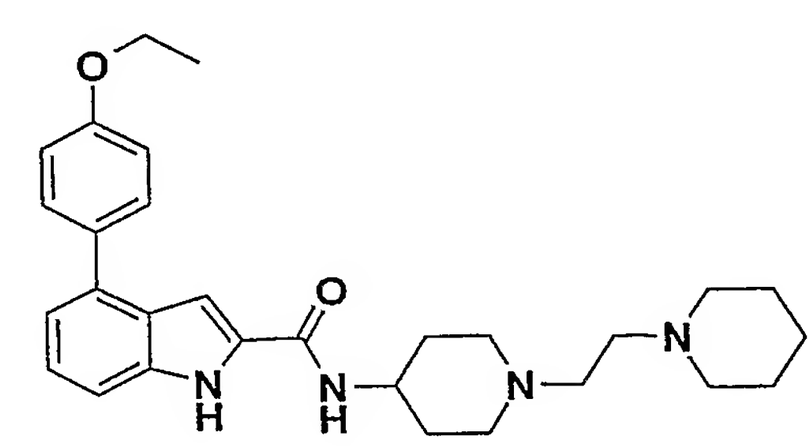
1. 4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and (4-ethoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 487 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.57 (d, 2H), 7.38 (d, 1H), 7.32 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.07 (q, 2H), 3.75 (m, 1H), 2.85 (m, 2H), 2.50-2.58 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.58 (m, 8H), 1.38 (t, 3H).

Example 60

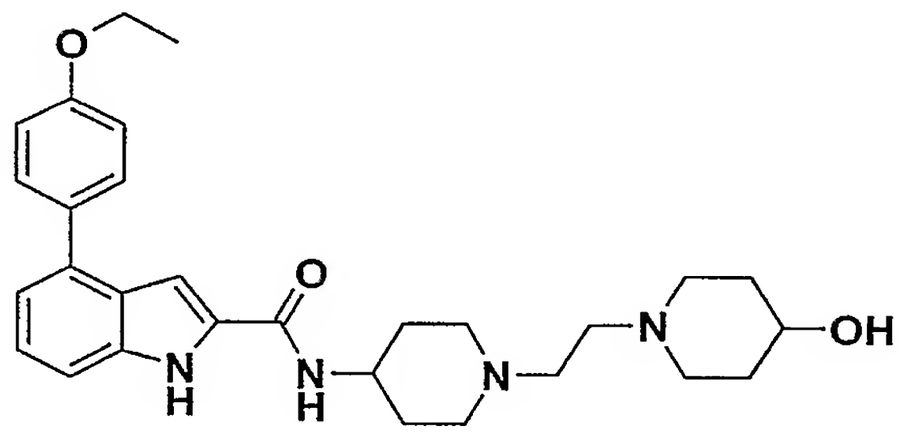
1. 4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **53** and (4-ethoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 475 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 2.87 (m, 2H), 2.25-2.4 (m, 8H), 2.0 (m, 2H), 1.75 (m, 2H), 1.3-1.57 (m, 8H), 1.38 (t, 3H).

Example 61

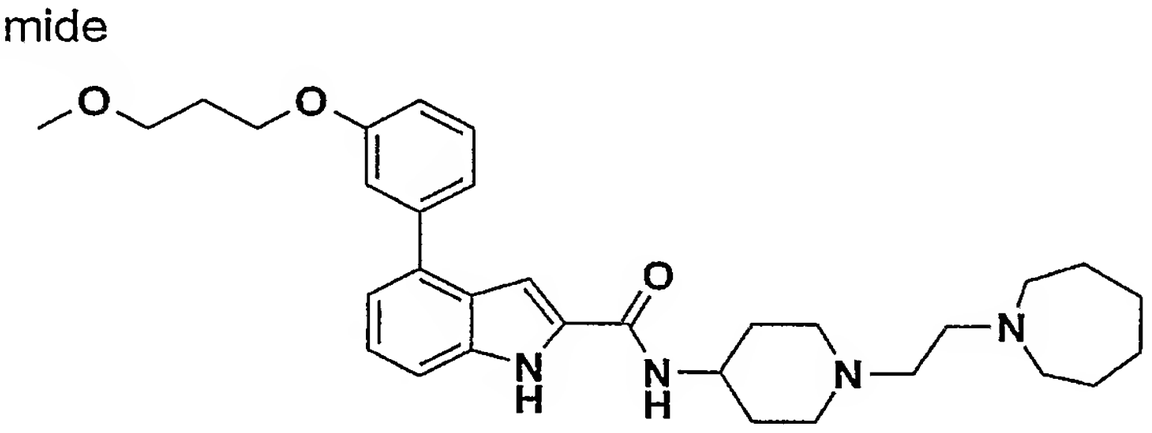
1. 4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound **54** and (4-ethoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 491 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.24 (d, 1H), 7.54 (d, 2H), 7.34 (d, 1H), 7.3 (s, 1H), 7.19 (dd, 1H), 7.06 (d, 2H), 7.0 (d, 1H), 4.47 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 3.40 (m, 1H), 2.85 (m, 2H), 2.68 (m, 2H), 2.36 (m, 4H), 1.98 (m, 4H), 1.74 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.37 (t, 3H), 1.32 (m, 2H).

Example 62

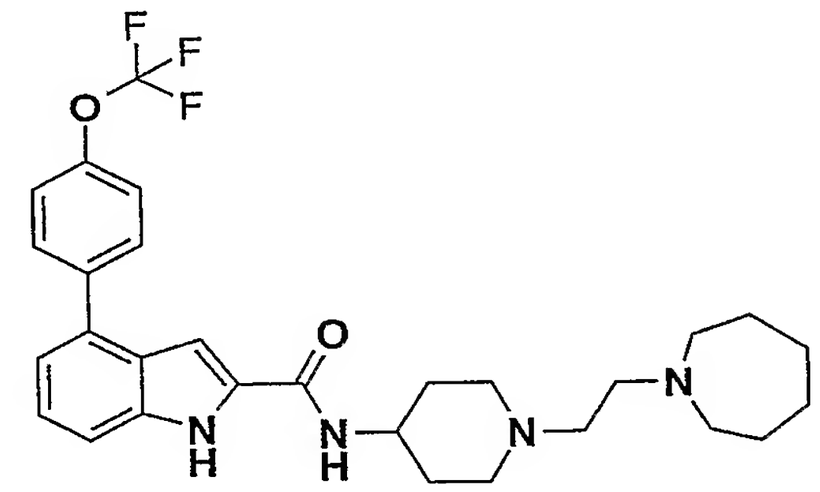
1. 4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and [3-(3-methoxy-propoxy)-phenyl]-boronic acid analogous to the method described in example **50**.
MS (ESI): 533.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.28 (d, 1H), 7.38-7.43 (m, 2H), 7.32 (s, 1H), 7.2-7.25 (m, 2H), 7.15 (m, 1H), 7.08 (d, 1H), 6.95 (dd, 1H), 4.1 (t, 2H), 3.75 (m, 1H), 3.48 (t, 2H), 3.25 (s, 3H), 2.85 (m, 2H), 2.48-2.58 (m, 8H), 2.35 (m, 2H), 1.95-2.04 (m, 4H), 1.75 (m, 2H), 1.48-1.6 (m, 10H).

Example 63

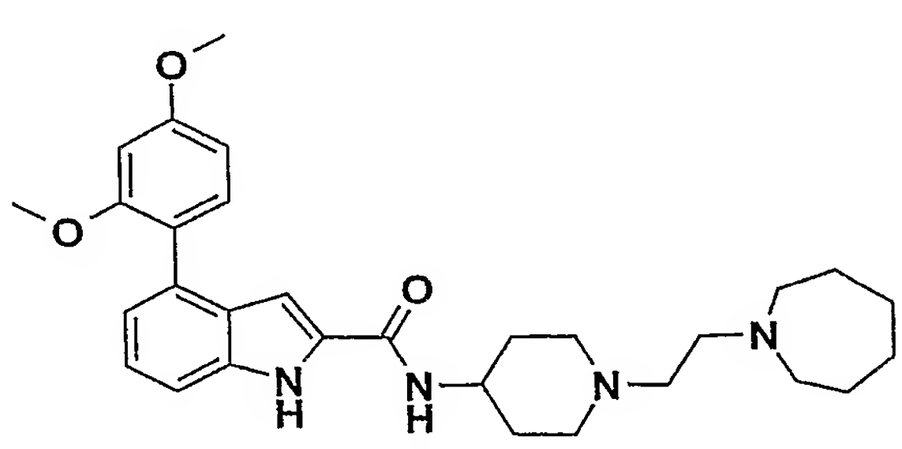
1. 4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and 4-trifluoromethoxy-phenyl boronic acid analogous to the method described in example **50**.
MS (ESI): 529 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.28 (d, 1H), 7.78 (d, 2H), 7.50 (d, 2H), 7.44 (d, 1H), 7.3 (s, 1H), 7.25 (dd, 1H), 7.08 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5 - 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.6 (m, 10H).

Example 64

1. 4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

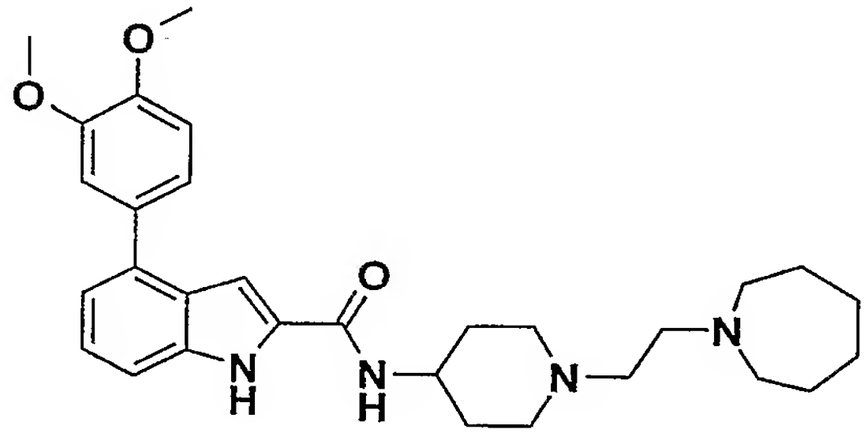


This compound is synthesized from compound **52** and (2,4-dimethoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 505.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.15 (d, 1H), 7.34 (d, 1H), 7.2 (d, 1H), 7.15 (dd, 1H), 6.93 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.65 (dd, 1H), 3.84 (s,

3H), 3.73 (m, 1H), 3.68 (s, 3H), 2.85 (m, 2H), 2.47-2.58 (m, 8H), 2.35 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 8H).

Example 65

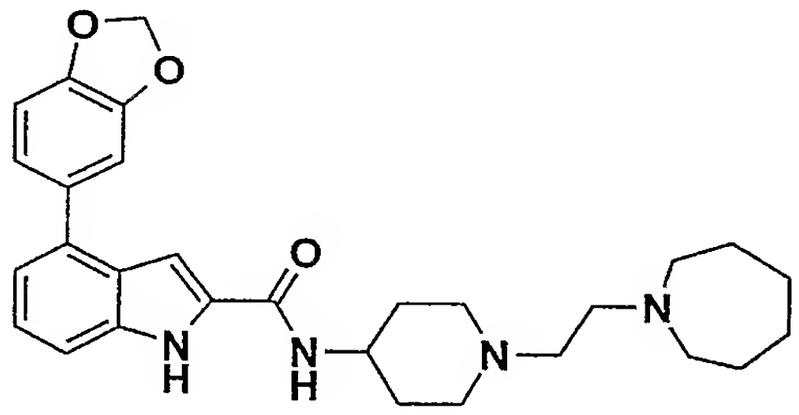
1. 4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and (3,4-dimethoxy-phenyl)-boronic acid analogous to the method described in example **50**.
MS (ESI): 505.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Example 66

1. 4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

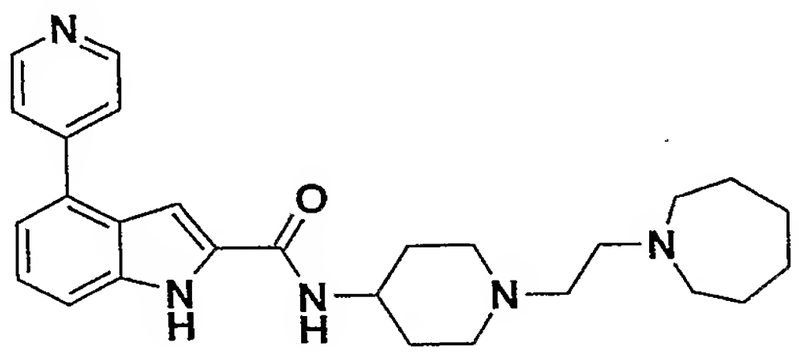


This compound is synthesized from compound **52** and benzo[1,3]dioxol-5-yl-boronic acid analogous to the method described in example **50**.
MS (ESI): 489.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.28 (d, 1H), 7.38 (d, 1H), 7.3 (m, 1H), 7.2 (d, 1H), 7.18 (m, 1H), 7.1 (dd, 1H), 7.04 (dd, 1H), 6.08 (s, 2H), 3.75 (m,

1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 67

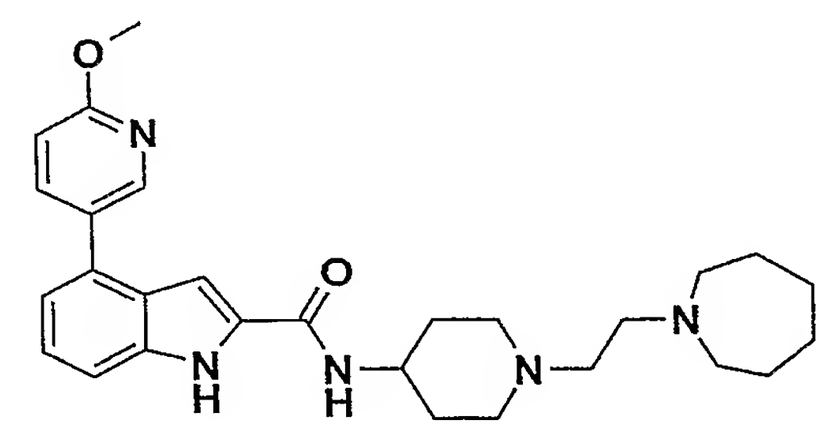
1. 4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and pyridin-4-yl-boronic acid analogous to the method described in example **50**.
MS (ESI): 446.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.68 (d, 2H), 8.3 (d, 1H), 7.68 (d, 1H), 7.5 (d, 1H), 7.38 (s, 1H), 7.3 (m, 1H), 7.2 (d, 1H), 3.75 (m, 1H), 2.88 (m, 2H), 2.45-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.6 (m, 10H).

Example 68

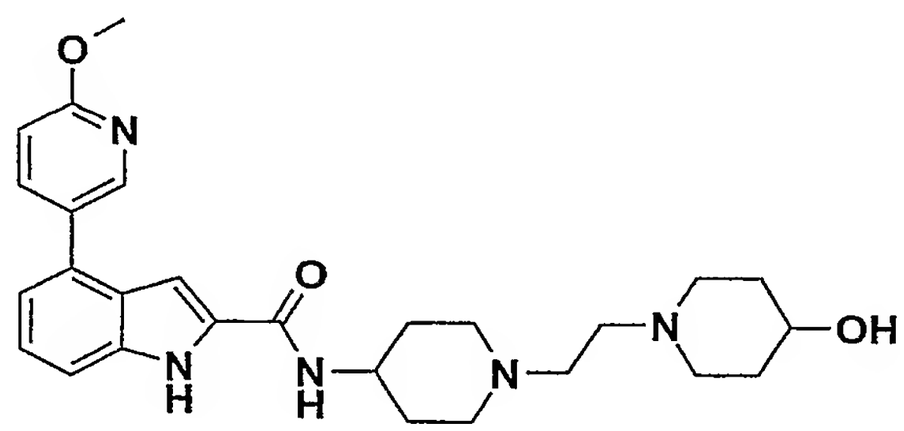
1. 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound **52** and (6-methoxy-pyridin-3-yl)-boronic acid acid analogous to the method described in example **50**.
MS (ESI): 476.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.48 (d, 1H), 8.3 (d, 1H), 7.98 (dd, 1H), 7.42 (d, 1H), 7.35 (s, 1H), 7.24 (dd, 1H), 7.08 (d, 1H), 6.97 (d, 1H), 3.93 (s, 3H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.35 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 69

1. 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

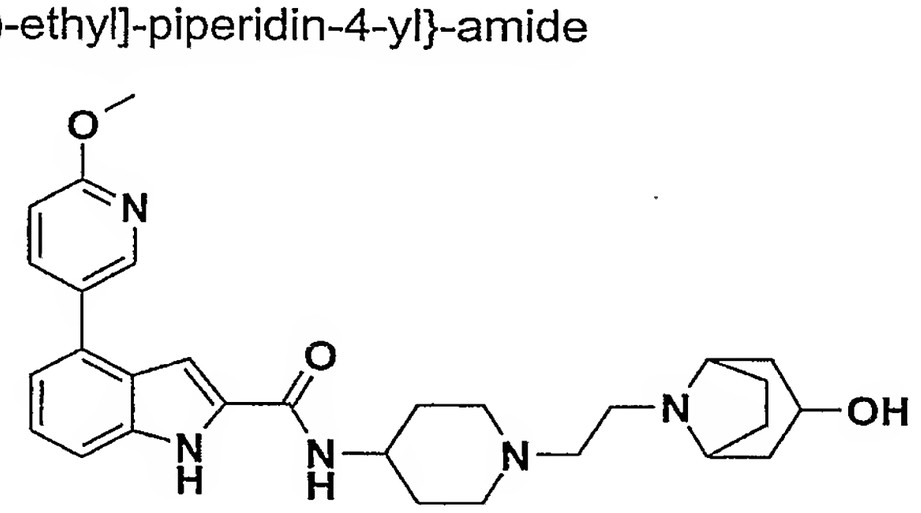


This compound is synthesized from compound **54** and (6-methoxy-pyridin-3-yl)-boronic acid analogous to the method described in example **50.**

MS (ESI): 478.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 8.47 (d, 1H), 8.27 (d, 1H), 7.95 (dd, 1H), 7.40 (d, 1H), 7.35 (s, 1H), 7.23 (dd, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 4.48 (d, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 3.39 (m, 1H), 2.85 (m, 2H), 2.68 (m, 2H), 2.36 (m, 4H), 1.99 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Example 70

1. 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide



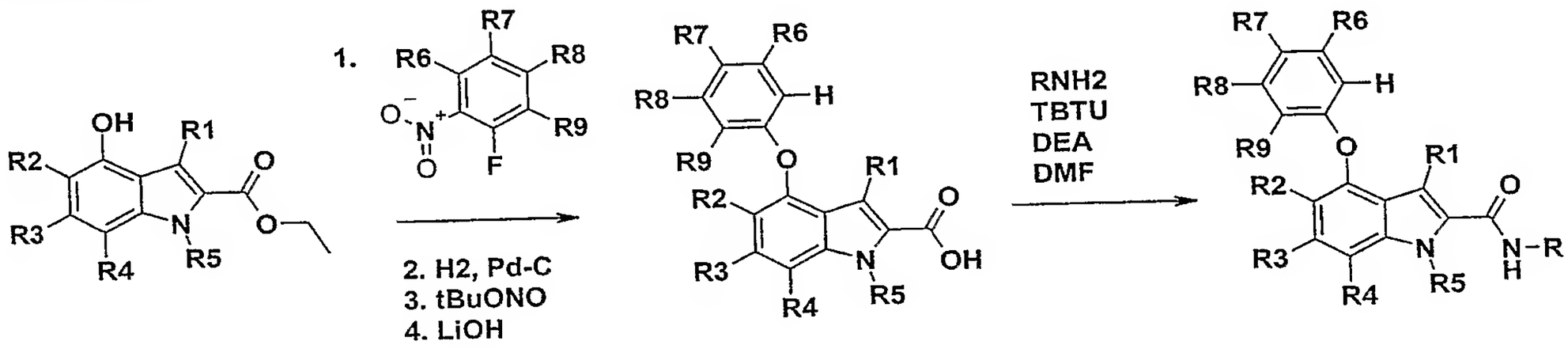
This compound is synthesized from compound **55** and (6-methoxy-pyridin-3-yl)-boronic acid analogous to the method described in example **50.**

MS (ESI): 504.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.48 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.4 (d, 1H), 7.35 (m, 1H), 7.23 (dd, 1H), 7.08 (d, 1H), 6.95 (d, 1H), 4.23

(br, 1H), 3.93 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.8 (m, 6H), 1.53 (m, 4H).

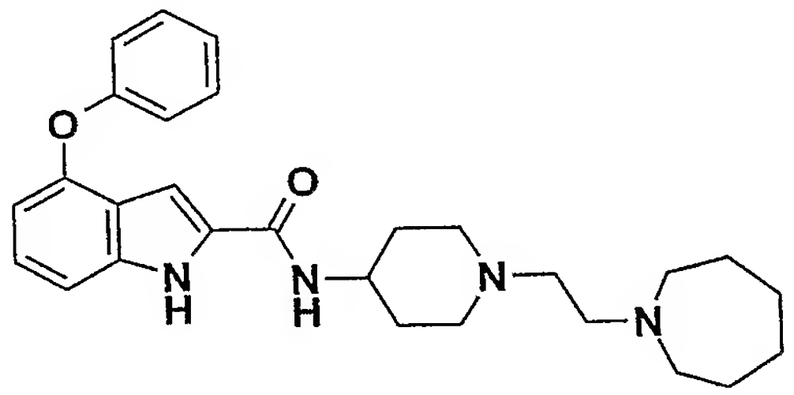
The 4-aryloxy-indole-2-carboxamides are generally prepared by a coupling of the 4-hydroxy-indole-2-carboxamides with the corresponding 1-fluoro-2-nitro-benzenes (reaction scheme 9).

Reaction Scheme 9:



Example 71

1. 4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-phenoxy-1H-indole-2-carboxylic acid **56** (preparation see below) and amine **6**.
MS (ESI): 459.4 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.22 (d, 1H), 7.34 (dd, 2H), 7.24 (d, 1H), 7.04-7.15 (m, 3H), 6.95 (d, 2H), 6.55 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.52 – 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (t, 4H), 1.72 (m, 2H), 1.48 (m, 8H).

Synthesis of 4-phenoxy-1H-indole-2-carboxylic acid (56):

(1) Step A: 4-(2-Nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**57**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (0.5 g, 2.436 mmol) and 2-fluoro-nitro-benzene (0.257 ml, 2.436 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (0.67 g, 4.87 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used as a beige solid in the next step without further purification.

MS (ESI): 325.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.1 (d, 1H), 7.6 (dd, 1H), 7.32 (m, 2H), 7.25 (dd, 1H), 7.03 (d, 1H), 6.85 (m, 1H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(2) Step B: 4-(2-Amino-phenoxy)-1H-indole-2-carboxylic acid ethyl (**58**)

57 (0.5 g, 1.532 mmol) is dissolved in 100 ml of ethanol and, after addition of Pd-C (100 mg), the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.

MS (ESI): 297 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.13 (m, 2H), 7.0 (s, 1H), 6.88 (m, 1H), 6.8 (dd, 1H), 6.75 (dd, 1H), 6.5 (m, 1H), 6.38 (m, 1H), 4.9 (br, 2H), 4.3 (q, 2H), 1.3 (t, 3H).

(3) Step C: 4-Phenoxy-1H-indole-2-carboxylic acid ethyl ester (**59**)

Tert-butyl nitrite (0.2 ml, 1.687 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **58** (0.5 g, 1.687 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (370 mg of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).

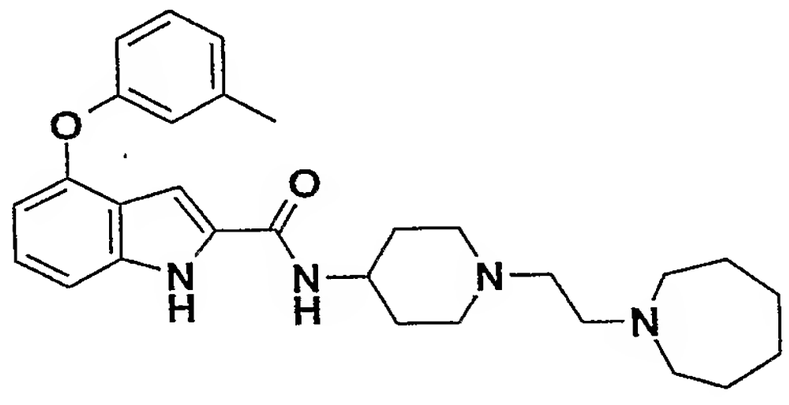
MS (ESI): 280.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.37 (d, 1H), 7.35 (d, 1H), 7.23 (m, 2H), 7.1 (dd, 1H), 7.0 (d, 2H), 6.82 (s, 1H), 6.6 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: -Phenoxy-1H-indole-2-carboxylic acid (**56**)

59 (160 mg, 0.569 mmol) is dissolved in 5 ml of methanol and treated with a solution of LiOH (27.2 mg, 1.138 mmol) in 3 ml of water. The mixture is stirred at room temperature overnight. Since the reaction is not complete (TLC), additional LiOH (30 mg, 1.25 mmol) is added and the stirring is continued for additional 18h. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 253 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.38 (d, 1H), 7.34 (d, 1H), 7.2 (m, 2H), 7.12 (m, 1H), 7.0 (d, 2H), 6.75 (s, 1H), 6.58 (d, 1H).

Example 72

1. 4-m-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-m-tolyloxy-1H-indole-2-carboxylic acid **60** (preparation see below) and amine **6**.
MS (ESI): 473.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.48 – 2.58 (m, 8H), 2.35 (m, 2H), 2.25 (s, 3H),1.98 (m, 2H), 1.75 (m, 2H), 1.48 – 1.55 (m, 8H).

Synthesis of 4-m-tolyloxy-1H-indole-2-carboxylic acid (60):

(1) Step A: 4-(5-Methyl-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**61**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 2-fluoro-4-methyl-1-nitro-benzene (756 mg, 4.87 mmol) are dissolved in 20 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room

temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
MS (ESI): 341 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 7.98 (d, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 7.15 (d, 1H), 6.88 (d, 1H), 6.63 (d, 1H), 4.3 (q, 2H), 2.28 (s, 3H),1.3 (t, 3H).

(2) Step B: 4-(2-Amino-5-methyl-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**62**)

61 (1.3 g, 3.82 mmol) is dissolved in 250 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
MS (ESI): 311 $[M+H]^+$]+, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (br, 1H), 7.13 (m, 2H), 7.03 (s, 1H), 6.72 (s, 2H), 6.58 (s, 1H), 6.37 (m, 1H), 4.68 (br, 2H), 4.3 (q, 2H), 2.08 (s, 3H), 1.3 (t, 3H).

(3) Step C: 4-m-Tolyloxy-1H-indole-2-carboxylic acid ethyl ester (**63**)

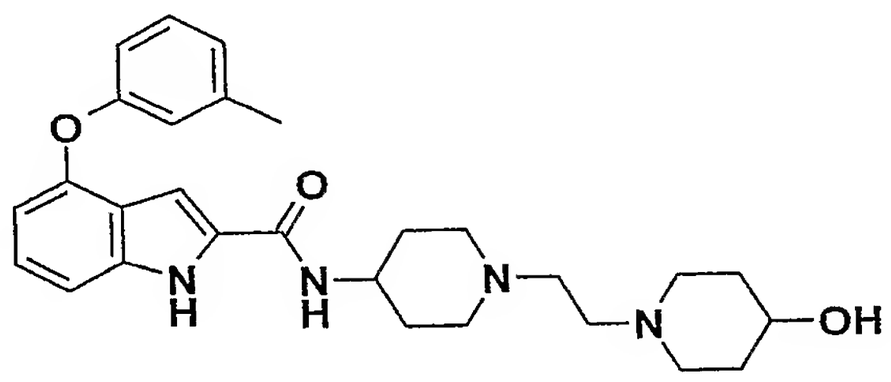
Tert-butyl nitrite (0.428 ml, 3.609 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **62** (1.1 g, 3.609 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (930 mg of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).
MS (ESI): 294.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.18-7.24 (m, 3H), 6.92 (m, 1H), 6.82 (m, 2H), 6.78 (dd, 1H), 6.58 (dd, 1H), 4.28 (q, 2H), 2.27 (s, 3H),1.3 (t, 3H).

(4) Step D: 4-m-Tolyloxy-1H-indole-2-carboxylic acid (**60**)

63 (520 mg, 1.761 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (84.3 mg, 3.52 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 266.1 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.15-7.25 (m, 3H), 6.9 (m, 1H), 6.84 (m, 1H), 6.78 (m, 2H), 6.57 (m, 1H), 2.27 (s, 3H).

Example 73

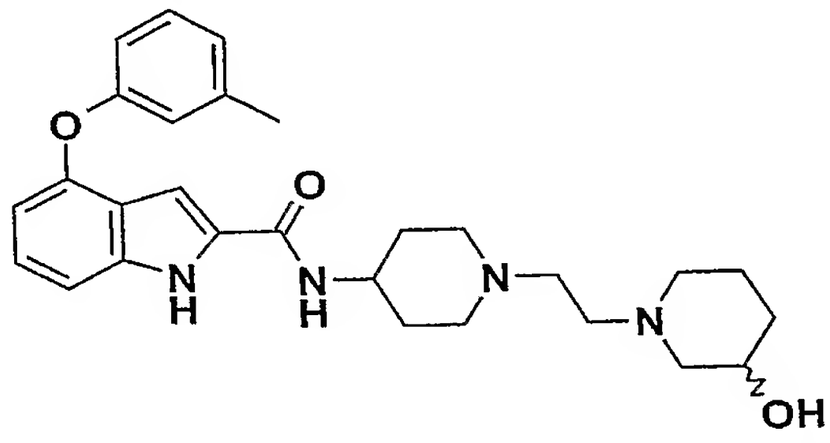
1. 4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-m-tolyloxy-1H-indole-2-carboxylic acid **60** and amine **9**.
MS (ESI): 477 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.28 (s, 3H),1.98 (m, 4H), 1.63-1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 74

1. 4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

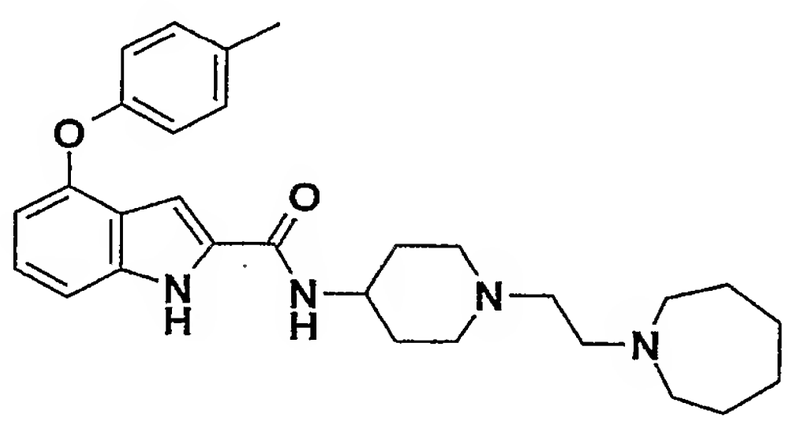


This compound is synthesized analogously to Example 1 from 4-m-tolyloxy-1H-indole-2-carboxylic acid **60** and racemic amine **22**.
MS (ESI): 477.3 $[M+H]^+$, 1H-NMR (80°C, DMSO-d_6): δ (ppm) 11.2 (s, 1H), 7.77 (d, 1H), 7.24 (dd, 1H), 7.2 (dd, 1H), 7.1 (ss, 1H), 7.04 (s, 1H), 6.88 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.54 (d, 1H), 3.75 (m, 1H), 3.5 (m, 1H), 2.7-2.9 (m, 4H), 2.6 (m, 1H), 2.44 (m, 4H), 2.3 (s,

3H),2.13 (m, 2H), 2.05 (m, 1H), 1.95 (m, 1H), 1.7-1.85 (m, 3H), 1.55-1.65 (m, 3H), 1.4 (m, 1H), 1.15 (m, 1H).

Example 75

1. 4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid **64** (preparation see below) and amine **6**.
MS (ESI): 473.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.18 (d, 1H), 7.05 – 7.2 (m, 5H), 6.85 (d, 2H), 6.47 (m, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47 – 2.58 (m, 6H), 2.35 (m, 2H), 2.25 (s, 3H),1.98 (m, 2H), 1.75 (m, 2H), 1.48 – 1.55 (m, 10H).

Synthesis of 4-p-tolyloxy-1H-indole-2-carboxylic acid (64):

(1) Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**65**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1-fluoro-4-methyl-2-nitro-benzene (0.6 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
MS (ESI): 341 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.88 (d, 1H), 7.45 (dd, 1H), 7.27 (d, 1H), 7.22 (dd, 1H), 6.98 (d, 1H), 6.87 (s, 1H), 6.6 (d, 1H), 4.3 (q, 2H), 2.35 (s, 3H),1.3 (t, 3H).

(2) Step B: 4-(2-Amino-4-methyl-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**66**)

65 (570 mg, 1.675 mmol) is dissolved in 150 ml of ethanol and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
MS (ESI): 311 $[M+H]^+$.

(3) Step C: 4-p-Tolyloxy-1H-indole-2-carboxylic acid ethyl ester (**67**)

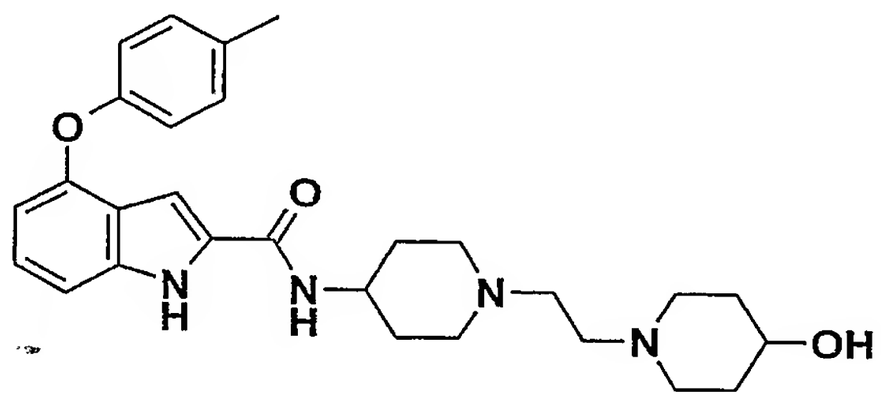
Tert-butyl nitrite (0.176 ml, 1.48 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **66** (460 mg, 1.48 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
MS (ESI): 294.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.15-7.24 (m, 4H), 7.4 (m, 2H), 6.85 (d, 1H), 6.52 (dd, 1H), 4.3 (q, 2H), 2.28 (s, 3H),1.3 (t, 3H).

(4) Step D: 4-p-Tolyloxy-1H-indole-2-carboxylic acid (**64**)

67 (70 mg, 0.237 mmol) is dissolved in 5 ml of methanol and treated with a solution of LiOH (11.4 mg, 0.474 mmol) in 3 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 266.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.8 (s, 1H), 7.13-7.2 (m, 4H), 6.9 (m, 2H), 6.77 (d, 1H), 6.52 (dd, 1H), 2.29 (s, 3H).

Example 76

1. 4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

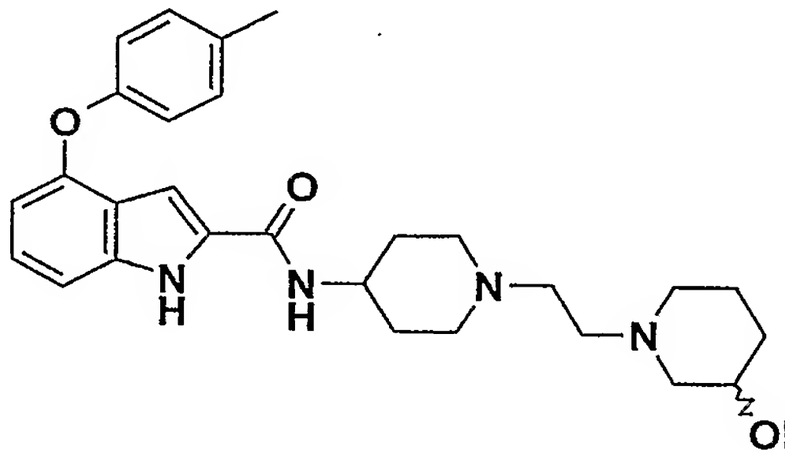


This compound is synthesized analogously to example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid **64** and amine **9**.

MS (ESI): 475.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8. 2 (d, 1H), 7.07-7.2 (m, 5H), 6.85 (d, 2H), 6.47 (d, 1H), 4.48 (br, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.27 (s, 3H), 1.95-2.05 (m, 4H), 1.65-1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 77

1. 4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

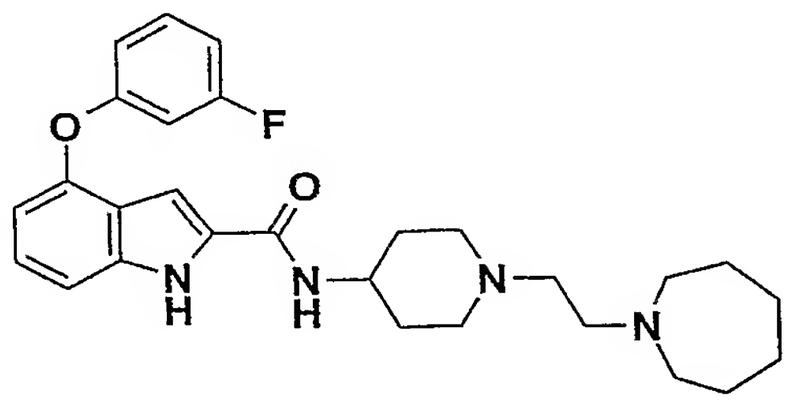


This compound is synthesized analogously to example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid **64** and racemic amine **22**.

MS (ESI): 475.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8. 2 (d, 1H), 7.08-7.2 (m, 5H), 6.87 (d, 2H), 6.47 (d, 1H), 4.53 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 3H), 2.65 (m, 1H), 2.37 (m, 4H), 2.28 (s, 3H), 1.98 (t, 2H), 1.7-1.85 (m, 5H), 1.55 (m, 3H), 1.35 (m, 1H), 1.05 (m, 1H).

Example 78

1. 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(3-fluoro-phenoxy)-1H-indole-2-carboxylic acid **68** (preparation see below) and amine **6**.
MS (ESI): 479.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.2 (d, 1H), 7.35 (dd, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.8 (m, 2H), 6.68 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5–2.58 (m, 6H), 2.35 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48 – 1.55 (m, 10H).

Synthesis of 4-(3-fluoro-phenoxy)-1H-indole-2-carboxylic acid (68):

(1) Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**69**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 2,4-difluoro-1-nitro-benzene (0.534 ml, 4.87 mmol) are dissolved in 20 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
MS (ESI): 343.1 $[M-H]^-$.

(2) Step B: 4 4-(2-Amino-5-fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**70**)

69 (1.6 g, 4.734 mmol) is dissolved in 250 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
MS (ESI): 315.2 $[M+H]^+$.

(3) Step C: 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**71**)

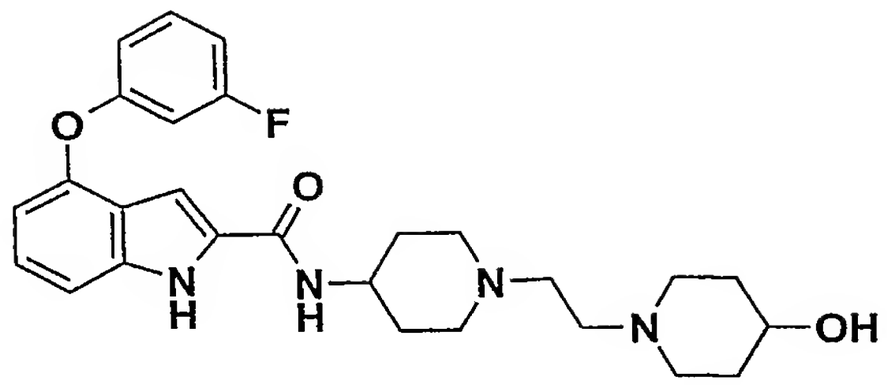
Tert-butyl nitrite (0.46 ml, 4.45 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **70** (1.4 g, 4.45 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.0 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).
MS (ESI): 298.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.35 (dd, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 6.92 (dd, 1H), 6.77-6.87 (m, 3H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid (**68**)

71 (440 mg, 1.47 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (70 mg, 1.47 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 270.1 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.95 (s, 1H), 11.9 (s, 1H), 7.35 (dd, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 6.9 (dd, 1H), 6.77-6.85 (m, 2H), 6.75 (s, 1H), 6.7 (d, 1H).

Example 79

1. 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

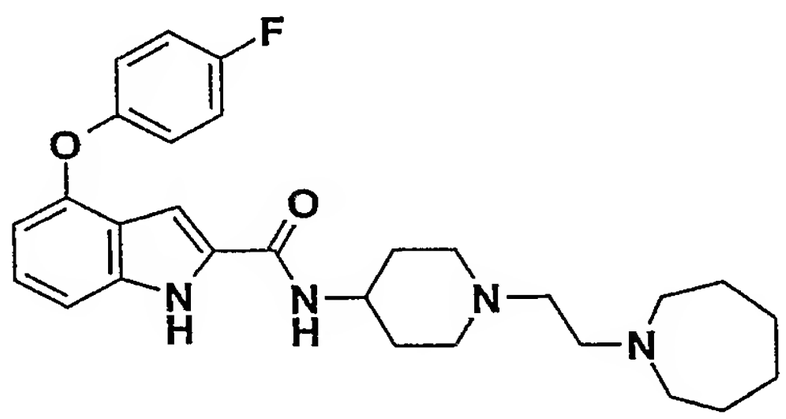


This compound is synthesized analogously to example 1 from 4-(3-fluoro-phenoxy)-1H-indole-2-carboxylic acid **68** and amine **9**.

MS (ESI): 479 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.21 (d, 1H), 7.35 (dd, 1H), 7.29 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.8 (m, 2H), 6.68 (d, 1H), 4.49 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H), 1.95 (m, 4H), 1.63-1.77 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 80

1. 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(4-fluoro-phenoxy)-1H-indole-2-carboxylic acid **72** (preparation see below) and amine **6**.

MS (ESI): 477.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.2 (d, 1H), 7.14-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5–2.6 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48 – 1.57 (m, 10H).

Synthesis of 4-(4-fluoro-phenoxy)-1H-indole-2-carboxylic acid (72):

(1) Step A: 4-(4-Fluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**73**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (0.92 g, 4.483 mmol) and 1,4-difluoro-2-nitro-benzene (0.486 ml, 4.483 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.2 g, 8.96 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
MS (ESI): 343.1 $[M-H]^-$]-, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.08 (m, 1H), 7.55 (m, 1H), 7.3 (d, 1H), 7.24 (dd, 1H), 7.15 (dd, 1H), 6.9 (s, 1H), 6.62 (d, 1H), 4.3 (q, 2H), 1.32 (t, 3H).

(2) Step B: 4-(2-Amino-4-fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**74**)

73 (1.5 g, 4.21 mmol) is dissolved in 200 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
MS (ESI): 313.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.12 (m, 2H), 7.05 (m, 1H), 6.75 (dd, 1H), 6.58 (dd, 1H), 6.34 (m, 1H), 6.28 (dt, 1H), 5.25 (br, 2H), 4.3 (q, 2H), 1.32 (t, 3H).

(3) Step C: 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**75**)

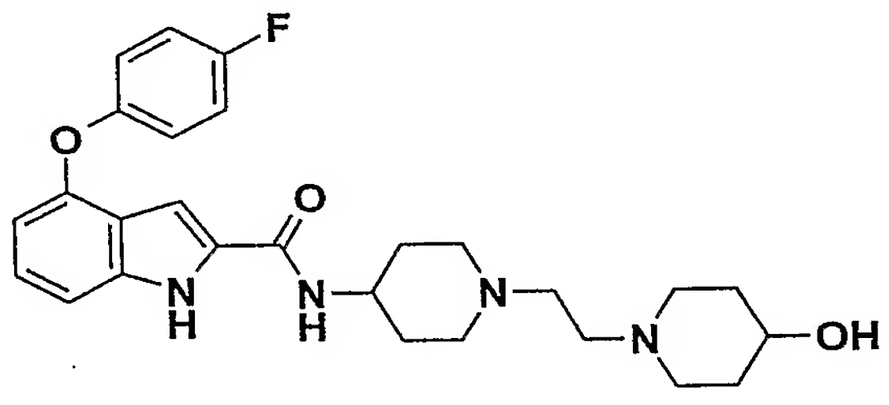
Tert-butyl nitrite (0.46 ml, 4.45 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **74** (1.4 g, 4.45 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.0 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).
MS (ESI): 298.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.2 (m, 4H), 7.05 (m, 2H), 6.85 (m, 1H), 6.54 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid (**72**)

75 (510 mg, 1.7 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (82 mg, 3.4 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 270.1 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 11.9 (s, 1H), 7.15-7.22 (m, 4H), 7.05 (m, 2H), 6.78 (m, 1H), 6.55 (d, 1H).

Example 81

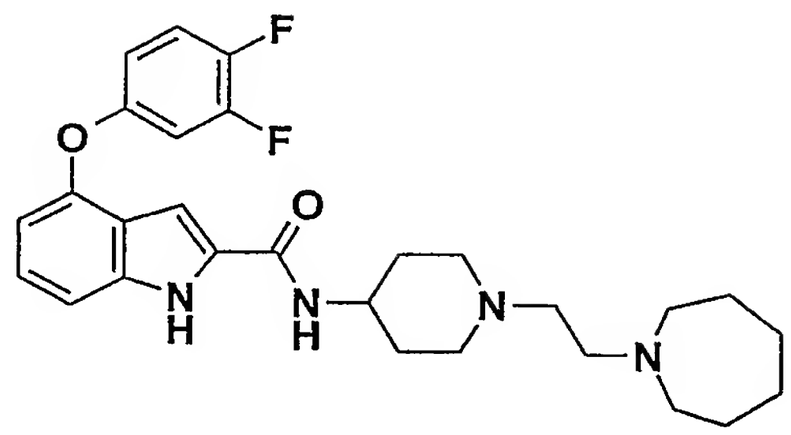
1. 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-fluoro-phenoxy)-1H-indole-2-carboxylic acid **72** and amine **9**.
MS (ESI): 479 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.1-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 4.46 (br, 1H), 3.72 (m, 1H), 3.42 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.64-1.77 (m, 4H), 1.53 (m, 2H), 1.35 (m, 2H).

Example 82

1. 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(3,4-difluoro-phenoxy)-1H-indole-2-carboxylic acid **76** (preparation see below) and amine **6**.

MS (ESI): 495.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.23 (d, 1H), 7.44 (m, 1H), 7.26 (d, 1H), 7.14 (m, 1H), 7.0 (m, 1H), 6.80 (m, 1H), 6.56 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 – 1.55 (m, 10H).

Synthesis of 4-(3,4-difluoro-phenoxy)-1H-indole-2-carboxylic acid (76):

(1) Step A: 4-(3,4-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**77**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1,2,4-trifluoro-5-nitro-benzene (0.559 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated.

MS (ESI): 361.1 $[M-H]^-$.

(2) Step B: 4-(2-Amino-4,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**78**)

77 (1.8 g, 4.87mmol) is dissolved in 150 ml of ethyl acetate and, after addition of Pd-C (500 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.

MS (ESI): 333.2 $[M+H]^+$.

(3) Step C: 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**79**)

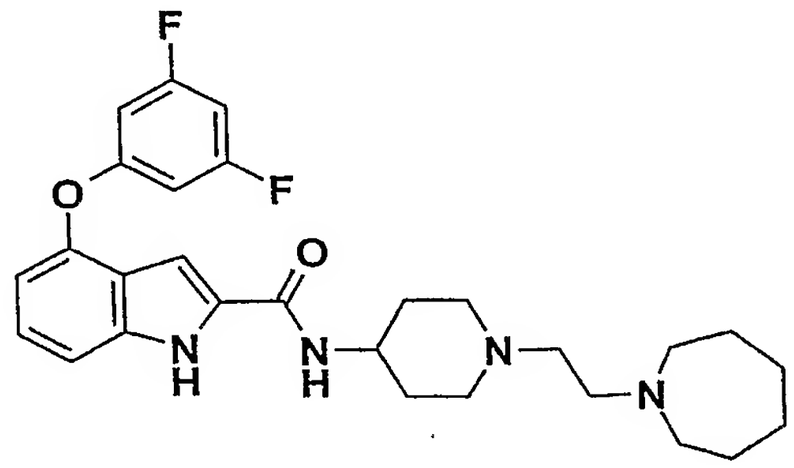
Tert-butyl nitrite (0.575 ml, 4.85 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **78** (1.6g, 4.85 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.78 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
MS (ESI): 316.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.45 (m, 1H), 7.27 (d, 1H), 7.2 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.95 (m, 1H), 6.55 (d, 1H), 4.3 (q, 2H), 1.34 (t, 3H).

(4) Step D: 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (**76**)

79 (380 mg, 1.2 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (57 mg, 2.4 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
MS (ESI): 288.1 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 12.0 (s, 1H), 7.45 (m, 1H), 7.25 (d, 1H), 7.18 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.87 (s, 1H), 6.55 (d, 1H).

Example 83

1. 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid **80** (preparation see below) and amine **6**.

MS (ESI): 495.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.21 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (d, 1H), 6.94 (m, 1H), 6.75 (d, 1H), 6.62 (m, 2H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47 – 2.58 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47 – 1.55 (m, 10H).

Synthesis of 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (80):

(1) Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**81**)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1,3,5-trifluoro-2-nitro-benzene (0.57 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated.
MS (ESI): 361.2 $[M-H]^-$.

(2) Step B: 4-(2-Amino-3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**82**)

81 (1.8 g, 4.87mmol) is dissolved in 150 ml of ethyl acetate and, after addition of Pd-C (500 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
MS (ESI): 333.2 $[M+H]^+$.

(3) Step C: 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (**83**)

Tert-butyl nitrite (0.547 ml, 4.6 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of **82** (1.5g, 4.6 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.5 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).

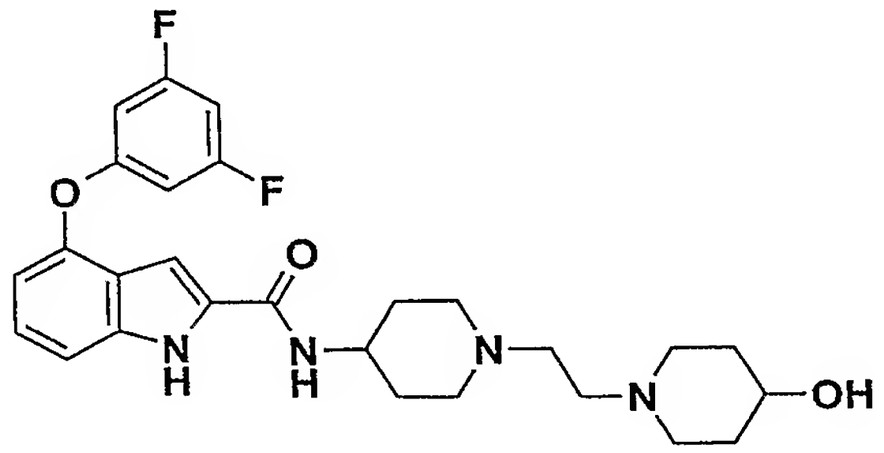
MS (ESI): 316.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.2 (s, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 6.95 (m, 1H), 6.82 (d, 1H), 6.79 (d, 1H), 6.68 (dd, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (**80**)

83 (260 mg, 0.82 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (40 mg, 1.6 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.

Example 84

1. 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

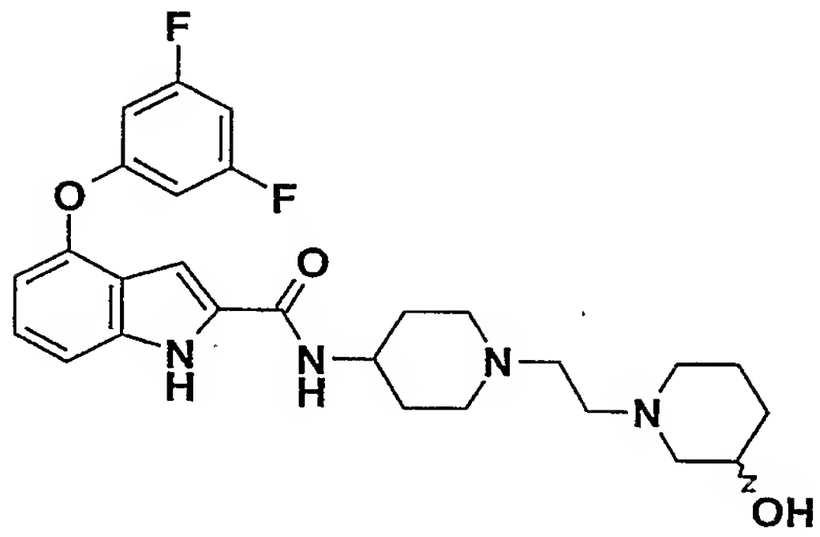


This compound is synthesized analogously to example 1 from 4-(3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid **80** and amine **9**.

MS (ESI): 497.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.79 (s, 1H), 8.22 (br, 1H), 7.32 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.9 (dd, 1H), 6.75 (d, 1H), 6.6 (d, 2H), 4.46 (s, 1H), 3.72 (m, 1H), 3.39 (m, 1H), 2.83 (m, 2H), 2.67 (m, 2H), 2.35 (m, 4H), 1.98 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.35 (m, 2H).

Example 85

1. 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

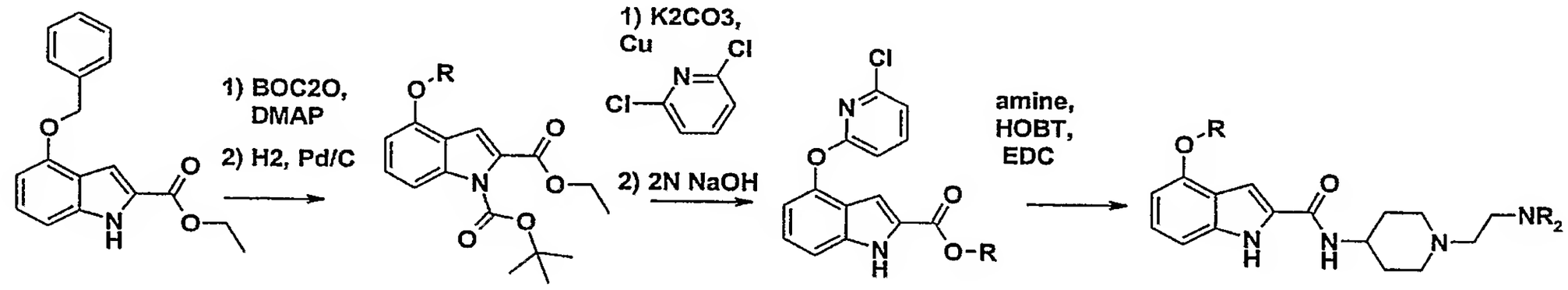


This compound is synthesized analogously to example 1 from 4-(3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid **80** and racemic amine **22**.

MS (ESI): 499 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.25 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.92 (dd, 1H), 6.76 (d, 1H), 6.63 (d, 2H), 4.02 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.8-2.9 (m, 3H), 2.67 (m, 2H), 2.38 (m, 4H), 1.99 (m, 2H), 1.68-1.88 (m, 5H), 1.47-1.6 (m, 3H), 1.371 (m, 1H), 1.05 (m, 1H).

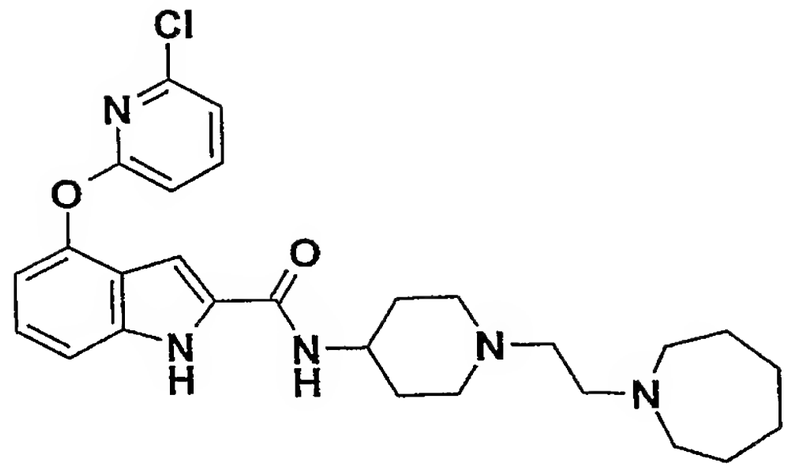
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 10.

Reaction Scheme 10:



Example 86

1. 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 4-(6-chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid **84** (preparation see below) and amine **6**.

MS (ESI): 494.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.2 (d, 1H), 7.85 (dd, 1H), 7.3 (d, 1H), 7.2 (m, 2H), 6.95 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.5 – 2.6 (m, 6H), 2.35 (m, 2H), 2.0 (t, 2H), 1.75 (m, 2H), 1.5 (m, 10H).

Synthesis of 4-(6-chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid (84):

(1) Step A: 4-Benzyloxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (**85**)

4-Benzyloxy-1H-indole-2-carboxylic acid ethyl ester (10 g, 34 mmol) and DMAP (80 mg) are dissolved in 80 ml of ethyl acetate. BOC2O (8.9 g, 41 mmol) dissolved in a small amount of ethyl acetate is added at room temperature. The mixture is stirred over night at room temperature. Then the reaction mixture is washed with 1m aqueous tartaric acid, water and brine. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
1H-NMR (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3 – 7.5 (m, 7H), 6.75 (d, 1H), 5.2 (s, 2H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(2) Step B: 4-Hydroxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (**86**)

85 (8 g, 20 mmol) is dissolved in 80 ml of ethyl acetate and, after addition of 5% Pd-C (700 mg), the mixture is hydrogenated at room temperature for 7 hours. The mixture is filtrated over celite to remove the catalyst and evaporated. The solid is suspended in ether/hexane and filtered.

Yield: 4.6 g (74%). 1H-NMR (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3 (m, 2H), 6.7 (d, 1H), 5.5 (s, 1H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(3) Step C: 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid ethyl ester (**87**)

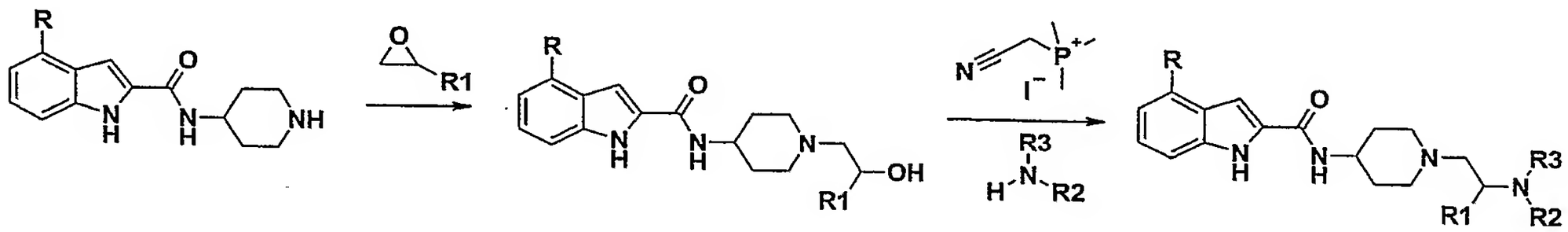
86 (500 mg, 1.6 mmol), 2,6-dichloro-pyridine (360 mg, 24 mmol) are dissolved in 15 ml of dimethylformamide. After addition of potassium carbonate (340 mg, 24 mmol) and a catalytic amount Cu-powder the mixture is heated to 160°C for 3 hours. The reaction mixture is cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layers are dried over sodium sulphate and evaporated. The crude product is solved in dichloromethane and after evaporation crystallized with cyclohexane.
MS (ESI): 317.2 $[M+H]^+$, 1H-NMR (CDCl3): δ (ppm) 9.2 (br, 1H), 7.7 (dd, 1H), 7.3 (m, 2H), 7.1 (m, 2H), 6,95 (dd, 1H), 6.75 (d, 1H), 4.4 (q, 2H), 1.4 (t, 3H).

(4) Step D: 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid (**84**)

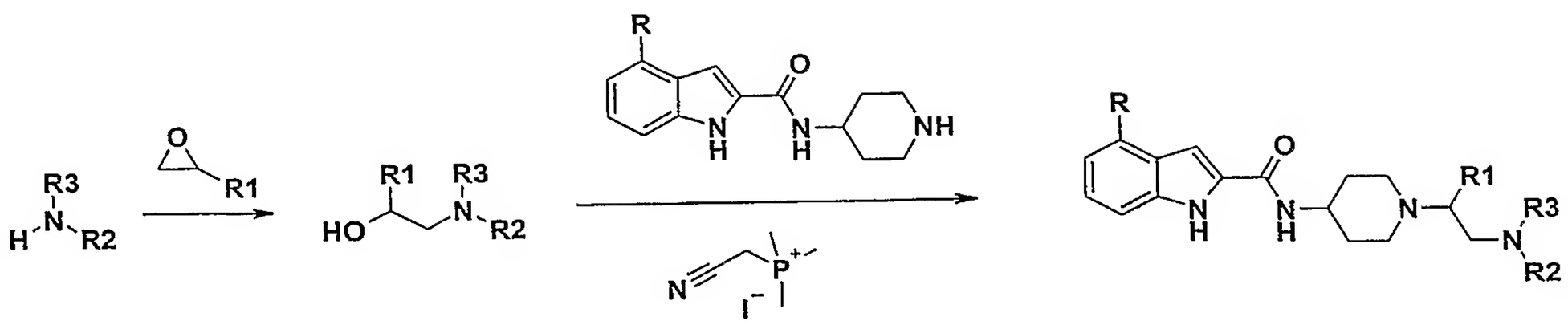
87 (100 mg, 0.315 mmol) is dissolved in 4 ml of methanol and treated with a solution of NaOH (1 ml , 2N). The mixture is stirred 1 hour at room temperature. The reaction mixture is acidified with HCl (1 ml, 2N) and evaporated. The crude mixture is used in the next step without further purification.

Indole-2-carboxamides with branched amines could for instance be prepared by oxirane opening reactions (Reaction Scheme 11 and 12).

Reaction Scheme 11:

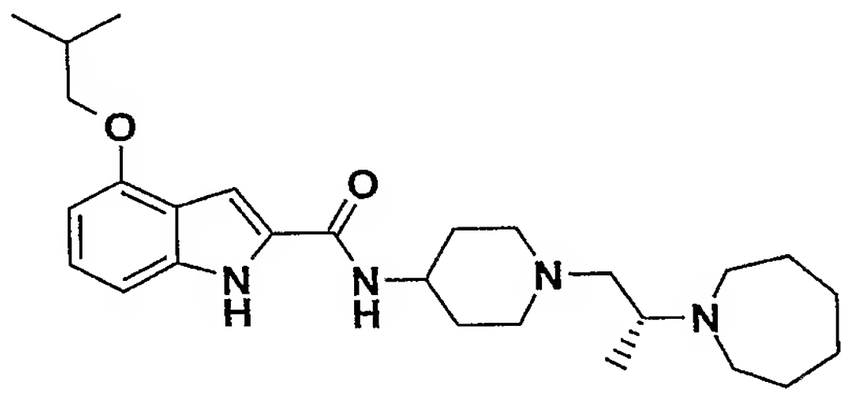


Reaction Scheme 12:



Example 87

1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2R-azepan-1-yl-propyl)-piperidin-4-yl]-amide



(1) Step A: 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2R-hydroxy-propyl)-piperidin-4-yl]-amide (**88**)

A solution of the hydrochloride of 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (**51**) from Example 42 (300 mg, 0.85 mmol) in 5 ml of ethanol and triethylamine (0.472 ml, 3.4 mmol) is treated with R(+)-propylene oxide (0.59 ml, 4.25 mmol) and stirred at room temperature in a sealed vessel for 14 hours. Another portion of R(+)-propylene oxide (0.59 ml, 4.25 mmol) is added and stirring continued for 24 hours. The solvents are then evaporated. The crude is re-dissolved in DCM and washed with 2N-NaOH and brine. The organic layer is dried over anhydrous sodium sulphate and evaporated to give a white powder.

MS (ESI): 374.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.22 (d, 1H), 7.22 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.25 (br s, 1H), 3.84 (d, 2H), 3.75 (overlapping m, 2H), 2.87 (m, 2H), 1.98-2.39 (m, 5H), 1.76 (m, 2H) 1.58 (m, 2H), 1.05 (m, 9H).

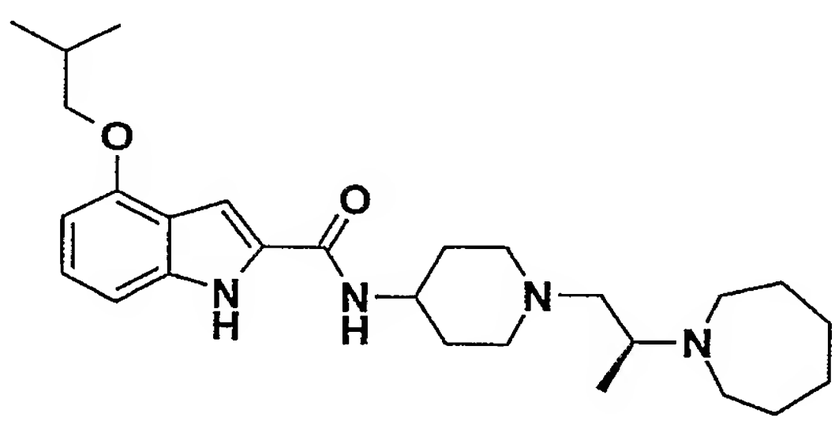
(2) Step B: 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2R-azepan-1-yl-propyl)-piperidin-4-yl]-amide

The alcohol (**88**) from above (100 mg, 0.27 mmol) is mixed with azepane (0.033 ml, 0.297 mmol), DIEA (0.227 ml, 1.35 mmol) and cyanomethyl-triphenyl phosphonium iodide (156 mg, 0.648 mmol) in 2 ml of propionitrile. The suspension is heated at 90 ^{0}C for 3 hours. The resulting solution is cooled, diluted with EtOAc, washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated. The crude material is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 10%).

MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 3.84 (d, 2H), 3.72 (br m, 1H), 2.52-2.95 (m, 8H), 2.15-2.4 (m, 3H), 2.1 (m, 1H), 1.77 (m, 2H), 1.45-1.67 (m, 10H) 1.05 (d, 6H), 0.95 (d, 3H).

Example 88

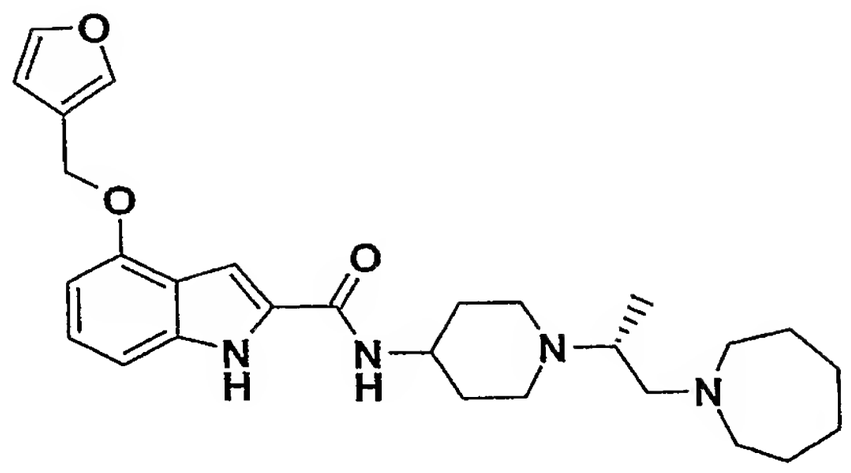
1. 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2S-azepan-1-yl-propyl)-piperidin-4-yl]-amide



The title compound is prepared as described in Example 87 from 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (**51**), S(-)-propylene oxide and azepane. Intermediate 4-isobutoxy-1H-indole-2-carboxylic acid [1-(2S-hydroxy-propyl)-piperidin-4-yl]-amide and final product had MS and NMR spectra identical to the (R)-enantiomers of Example 87.

Example 89

1. 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1R-methyl-ethyl)-piperidin-4-yl]-amide



(1) Step A: 4-{[4-(Furan-3-ylmethoxy)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (**89**)

To a solution of 4-(furan-3ylmethoxy)-1H-indole-2-carboxylic acid (**39**) from Example 16 (5 g, 19.44 mmol) in 10 ml of DCM is added 4-amino-piperidine-1-carboxylic acid tert-butyl ester (3.89 g, 19.44 mmol), HOBT (2.98 g, 19.44 mmol), triethylamine (5.4 ml, 38.88 mmol) and EDC (3.73 g, 19.44 mmol). The mixture is stirred at room temperature over night. It is then washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated to give a yellow powder. The crude material is purified by chromatography on silicagel using DCM and EtOAc (from 0% to 10%).
MS (ESI): 438.3 $[M-H]^-$, 1H-NMR ($CDCl_3$): δ (ppm) 9.42 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.21 (t, 1H), 7.05 (d, 1H), 6.96 (s, 1H), 6.6 (d, 1H), 6.55 (s, 1H), 6.08 (d, 1H), 5.07 (d, 2H), 4.04-4.2 (overlapping m, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H) 1.42 (m, 2H).

(2) Step B: 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (**90**)

The tert-butyl ester (**89**) from above (695 mg, 1.58 mmol) is dissolved in 5 ml of dioxane. A 4M-solution of HCl in dioxane (3.2 ml, 12.8 mmol) is added and the mixture is stirred for 24 hours. Evaporation gives the hydrochloride as a white powder.
MS (ESI): 340.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 9.0 (br m, 2H), 8.5 (d, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.3 (s, 1H), 7.09 (t, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 6.64 (s, 1H), 5.05 (d, 2H), 4.07 (m, 1H), 3.31 (m, 2H), 3.0 (m, 2H), 1.96 (m, 2H), 1.78 (m, 2H).

(3) 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1R-methyl-ethyl)-piperidin-4-yl]-amide

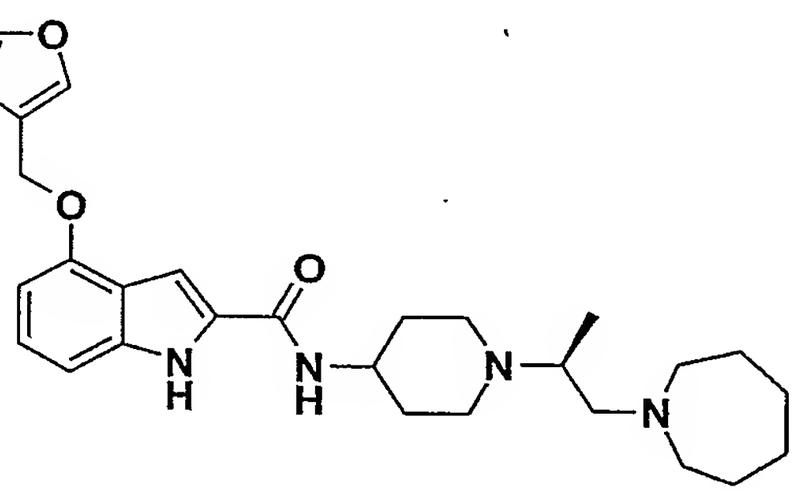
S(-)-propylene oxide (21.2 ml, 302.5 mmol) and azepam (3.41 ml, 30.25 mmol) are mixed in 10 ml of ethanol and stirred in a sealed vessel for 24 hours. The solvents are then evaporated and the crude oil of 1-azepan-1-yl-propan-2-ol (**91**) is used as such without further purification.

The alcohol (**91**) from above (63 mg, 0.405 mmol) is mixed with 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (**90**) from step B (100 mg, 0.27 mmol), DIEA (0.227 ml, 1.35 mmol) and cyanomethyl-triphenyl phosphonium iodide (193 mg, 0.81 mmol) in 2 ml of propionitrile. The suspension is heated at 90 °C for 3 hours. The resulting solution is cooled, diluted with EtOAc, washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated. The crude material is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 10%).

MS (ESI): 479.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 5.03 (d, 2H), 3.72 (m, 1H), 2.75-2.95 (m, 3H), 2.58 (m, 4H), 2.33 (m, 1H), 2.0-2.2 (m, 2H), 1.92 (m, 1H), 1.74 (m, 2H), 1.45-1.6 (m, 10H), 0.91 (d, 3H).

Example 90

1. 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1S-methyl-ethyl)-piperidin-4-yl]-amide



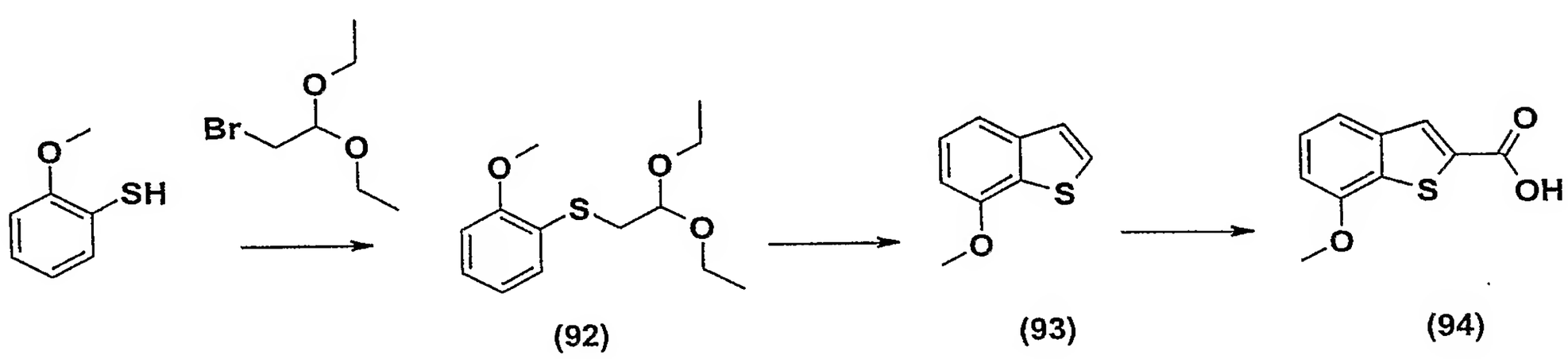
The title compound is prepared from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (**90**) as described in Example 89 using R(+)-propylene oxide instead of the (S)-enantiomer.

MS and NMR spectra are identical to its enantiomeric example 89.

Synthesis of the benzthiophene-2-carboxamides

The 7-alkoxy-benzthiophene-2-carboxylates are synthesized starting from 2-alkoxy-benzenethiol (reaction scheme 13).

Reaction Scheme 13:



(92) (93) (94)

(1) 1-(2,2-Diethoxy-ethylsulfanyl)-2-methoxy-benzene (**92**)

2-Methoxy-benzenethiol (3.65 ml, 30 mmol) is dissolved in 60 ml of acetone. After addition of potassium carbonate (4.15 g, 30 mmol) 2-bromo-1,1-diethoxy-ethane (4.66 ml, 30 mmol) is added dropwise. The reaction mixture is stirred for 72 h at r.t. Then the reaction mixture is filtrated and the filtrate is evaporated under reduced pressure. The crude product is dissolved in diethylether and washed with water, 0.5 M aqueous sodium hydroxide solution and saline. The combined aqueous layers are extracted with ether. The organic phases are dried over sodium sulfate and evaporated under reduced pressure.
MS (ESI): 256 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.25 (d, 1H), 7.18 (dd, 1H), 6.97 (d, 1H), 6.9 (dd, 1H), 4.58 (t, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.45 (m, 2H), 3.02 (d, 2H), 1.1 (t, 6H).

(2) 7-Methoxy-benzo[b]thiophene (**93**)

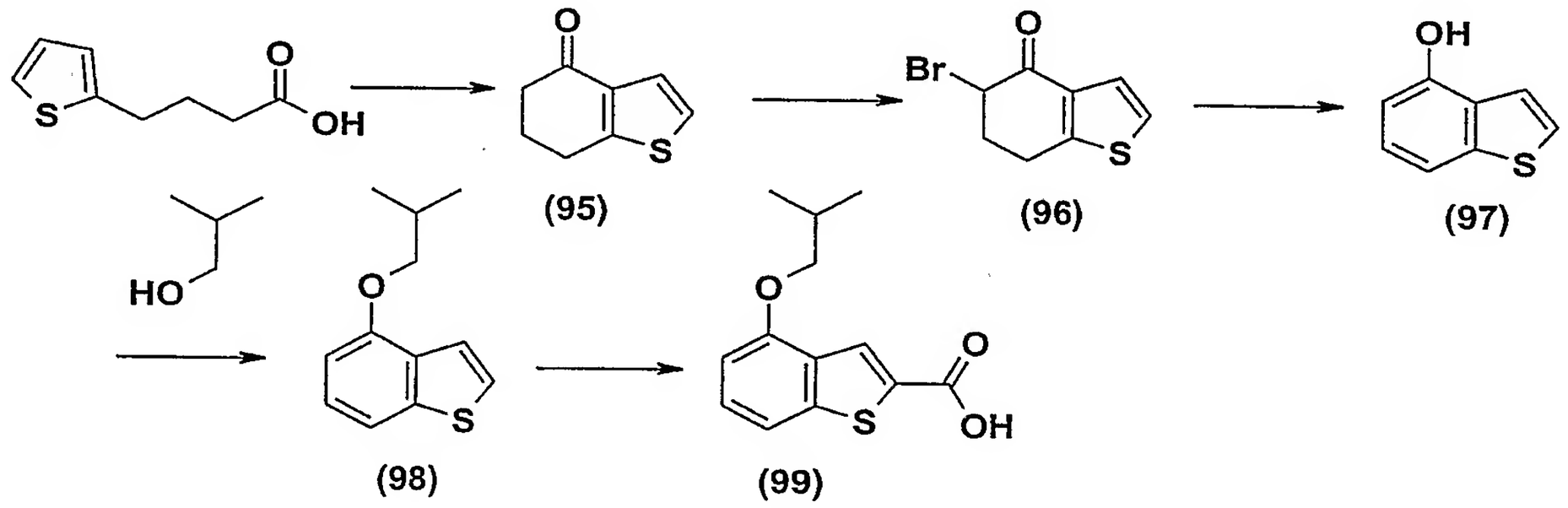
Polyphosphoric acid (4.32 ml, 58 mmol) is dissolved in 60 ml of chlorobenzene under argon, heated to 140°C and **92** is added dropwise. After stirring for 16 h at this temperature, the chlorobenzene layer is separated and evaporated. The crude product (1.05 g of a brown oil) is further purified by flash chromatography (silicagel; hexane / ethyl acetate 9:1).
MS (ESI): 164 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.7 (d, 1H), 7.46 (d, 1H), 7.42 (d, 1H), 7.33 (dd, 1H), 6.9 (d, 1H), 3.95 (s, 3H).

(3) 7-Methoxy-benzo[b]thiophene-2-carboxylic acid (**94**)

A 1.6M solution of butyllithium in hexane (0.84 ml, 1.34 mmol) is dissolved in 5 ml of dry diethyl ether under an argon atmosphere. A solution of **93** (200 mg, 1.22 mmol) in 2 ml of diethyl ether is added dropwise at room temperature. After 45 min heating under reflux, the mixture is cooled down to room temperature and added via syringe to a mixture of excess dry ice in ether, which has been dried by twice washing and decantation with diethyl ether. The reaction mixture is washed with water and acidified with 2M aqueous hydrochloric acid. The white precipitate is filtered off, washed with water and dried under high vacuum. MS (ESI): 206.9 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 13.5 (br s, 1H), 8.07 (s, 1H), 7.58 (d, 1H), 7.4 (dd, 1H), 7.05 (d, 1H), 3.96 (s, 3H).

The 4-alkoxy-benzthiophene-2-carboxylates are synthesized starting from 4-thiophen-2-yl-butyric acid (reaction scheme 14).

Reaction Scheme 14:



(1) 6,7-Dihydro-5H-benzo[b]thiophen-4-one (**95**)

Ortho-phosphoric acid (85%, 0.27 ml, 3.7 mmol) is dissolved in acetic acid anhydride (13 ml) and after addition of 4-thiophen-2-yl-butyric acid (9 g, 52.9 mmol) the mixture is stirred at 120°C for 2.5 h. The brown solution is cooled down using an ice bath, water is added and the reaction mixture is extracted with dichloromethane. The organic layers are washed with 2M NaOH solution and twice with water until a neutral pH is reached. The solution is dried over Na2SO4 and evaporated under reduced pressure. The crude product is obtained as a

brown oil (7.84 g), which is further purified by flash-chromatography (silica gel, ethyl acetate / hexane 9:1).
MS (ESI): 152 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.38 (d, 1H), 7.25 (d, 1H), 3.03 (t, 2H), 2.48 (m, 2H), 2.12 (t, 2H).

(2) 5-Bromo-6,7-dihydro-5H-benzo[b]thiophen-4-one (**96**)

6,7-Dihydro-5H-benzo[b]thiophen-4-one (**95**, 5.8 g, 38.3 mmol) is dissolved in 200 ml of dry diethyl ether and cooled down to -10°C. A solution of bromine (6.1 g, 38.3 mmol) in 30 ml of tetrachloromethane and 2-3 drops of diethyl ether is slowly added. The mixture is stirred for 15min at -10°C, 15min at 0°C and 18h at room temperature. Then water and diethyl ether is added slowly. The organic layers are washed with water, dried over Na2SO4 and evaporated.
MS (ESI): 230, 232 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.46 (d, 1H), 7.3 (d, 1H), 4.87 (dt, 1H), 3.1 (m, 2H), 2.45 (m, 2H).

(3) Benzo[b]thiophen-4-ol (**97**)

5-Bromo-6,7-dihydro-5H-benzo[b]thiophen-4-one (**96**, 77% pure, 8.7g, 28.9 mmol), LiBr (5.7 g, 65.1 mmol) and Li2CO3 (4.3 g, 57.8 mmol) are placed under argon in 300 ml of DMF and refluxed for 3 h. The reaction mixture is allowed to cool down to room temperature and evaporated under high vacuum. After addition of ice water and cold 2M aqueous HCl solution the mixture is extracted with diethyl ether. The organic layers are extracted with 2M NaOH and the combined aqueous layers are acidified with concentrated HCl. The product is extracted twice with ethyl acetate and the organic layers are washed with saturated NaCl solution, dried over Na2SO4 and evaporated under reduced pressure.
MS (ESI): 149.0 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 9.95 (br s, 1H), 7.55 (d, 1H), 7.45 (d, 1H), 7.38 (d, 1H), 7.15 (dd, 1H), 6.72 (d, 1H).

(4) 4-Isobutoxy-benzo[b]thiophene (**98**)

Benzo[b]thiophen-4-ol (**97**, 4.3 g, 28.9 mmol) and iso-butanol (3.2 ml, 34.7 mmol) are dissolved under argon in 150 ml of toluene. After addition of triphenylphosphine (9.1 g, 34.7 mmol) and a 40% solution of DEAD in toluene (16.8 ml, 34.7 mmol), the mixture is stirred at 120°C over night. After cooling down, the reaction mixture is subsequently washed with

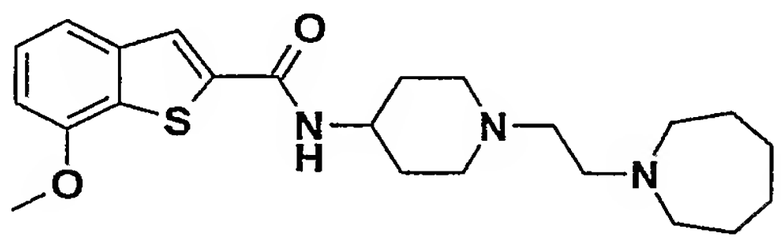
saturated aqueous NaHCO3 solution and NaCl solution, dried over Na2SO4 and evaporated under reduced pressure. Triphenylphosphinoxid is removed by crystallization from ethyl acetate and hexane and the crude product is further purified by flash chromatography (silica gel, hexane / ethyl acetate 9:1).
MS (ESI): 206 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.62 (d, 1H), 7.5 (d, 1H), 7.44 (d, 1H), 7.27 (dd, 1H), 6.85 (d, 1H), 3.88 (d, 2H), 2.12 (m, 1H), 1.05 (d, 6H).

(5) 4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid (**99**)

A 1.6 M solution of n-butyl lithium in hexane (18 ml, 28.8 mmol) is dissolved under an argon atmosphere in 100 ml of dry diethyl ether, followed by dropwise addition of a solution of 4-isobutoxy-benzo[b]thiophene (**98**, 5.4 g, 26.1 mmol) in 40 ml of diethyl ether. The reaction mixture is refluxed for 45 min, then cooled down and transferred via syringe to a mixture of excess dry ice (115g, 2.61 mol) in diethyl ether (the dry ice is washed before twice with diethyl ether). The mixture is allowed to stir overnight at room temperature, then distributed between diethyl ether and water. The ether layers are reextracted with water. The aqueous layers are acidified with 2M aqueous HCl solution, and the precipitate is filtered off, washed with water and dried under high vacuum.
MS (ESI): 250 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 13.4 (br s, 1H), 7.98 (s, 1H), 7.55 (d, 1H), 7.43 (dd, 1H), 6.9 (d, 1H), 3.9 (d, 2H), 2.14 (m, 1H), 1.05 (d, 6H).

Example 91

1. 7-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



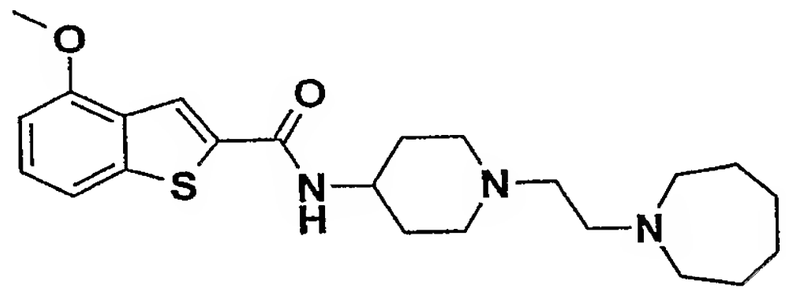
A solution of 7-methoxy-benzo[b]thiophene-2-carboxylic acid (**94**) (105 mg, 0.504 mmol), amine **6** (169 mg, 0.50 mmol) in 10 ml of DMF is treated with EDC (96.7 mg, 0.50 mmol), HOBT hydrate (85 mg, 0.55 mmol) and triethylamine (0.21 ml, 1.5 mmol) . The mixture is stirred over night and then evaporated under high vacuum. The crude residue is dissolved in ethyl acetate and washed twice with sodium bicarbonate (10%), brine and dried over sodium

sulfate. The crude product is then purified by recrystallization from ethyl acetate / diethyl ether.

MS (ESI): 416.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.5 (d, 1H), 8.07 (s, 1H), 7.48 (d, 1H), 7.37 (dd, 1H), 7.0 (d, 1H), 3.95 (s, 3H), 3.7 (br m, 1H), 2.87 (m, 2H), 2.35-2.7 (m, 10H), 2.05 (m, 2H), 1.78 (m, 2H), 1.47-1.64 (m, 8H).

Example 92

1. 4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

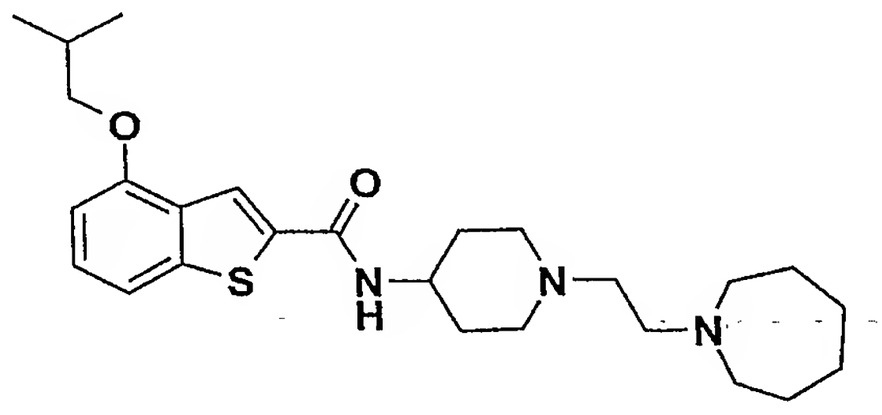


This compound is synthesized from 4-methoxy-benzo[b]thiophene-2-carboxylic acid and amine **6** analogous to the method described in Example **91**.

MS (ESI): 416.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.53 (d, 1H), 8.2 (s, 1H), 7.5 (d, 1H), 7.37 (dd, 1H), 6.9 (d, 1H), 3.94 (s, 3H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.6 (m, 10H).

Example 93

1. 4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

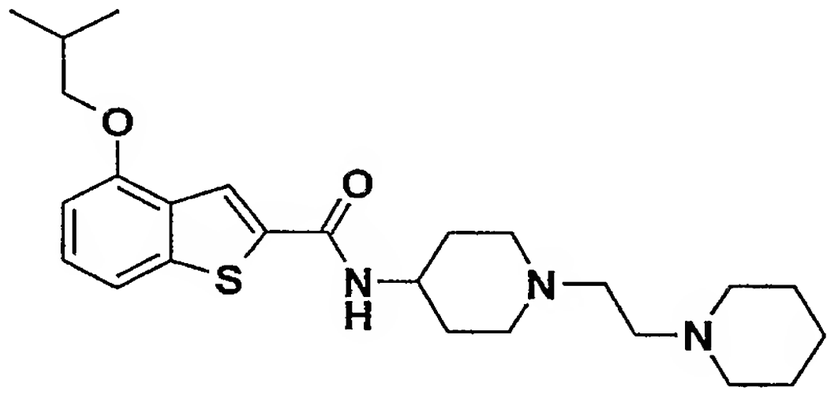


This compound is synthesized from compound **99** and amine **6** analogous to the method described in Example 91.

MS (ESI): 458.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.5 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.9 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.15 (m, 1H), 2.0 (m, 2H), 1.78 (m, 2H), 1.5-1.65 (m, 10H), 1.05 (d, 6H).

Example 94

1. 4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



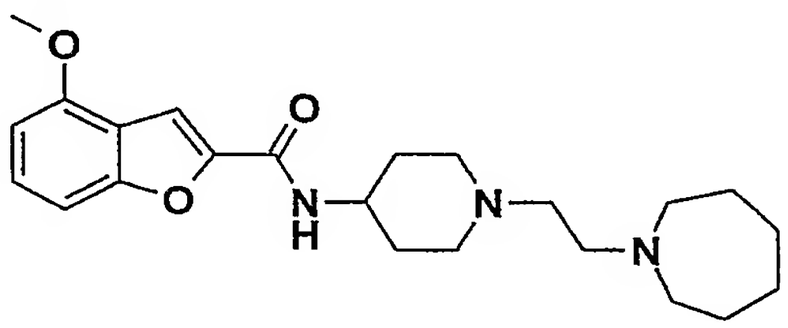
This compound is synthesized from compound **99** and amine **4** analogous to the method described in Example 91.

MS (ESI): 444.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.48 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.3 – 2.4 (m, 8H), 2.15 (m, 1H), 1.98 (m, 2H), 1.78 (m, 2H), 1.58 (m, 2H), 1.47 (m, 4H), 1.35 (m, 2H), 1.05 (d, 6H).

Synthesis of the benzofuran-2-carboxamides

Example 95

1. 4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

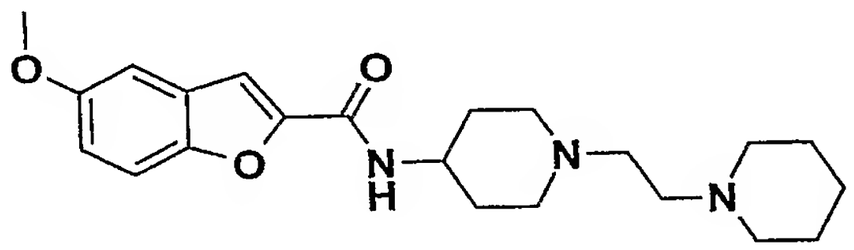


This compound is synthesized analogously to example 1 from 4-methoxy-benzofuran-2-carboxylic acid and amine **6**.

MS (ESI): 400.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.42 (d, 1H), 7.5 (s, 1H), 7.37 (t, 1H), 7.21 (d, 1H), 6.84 (d, 1H), 3.92 (s, 3H), 3.72 (m, 1H), 2.88 (m, 2H), 2.35-2.68 (m, 8H), 2.02 (m, 2H), 1.76 (m, 2H), 1.48-1.67 (m, 10H).

Example 96

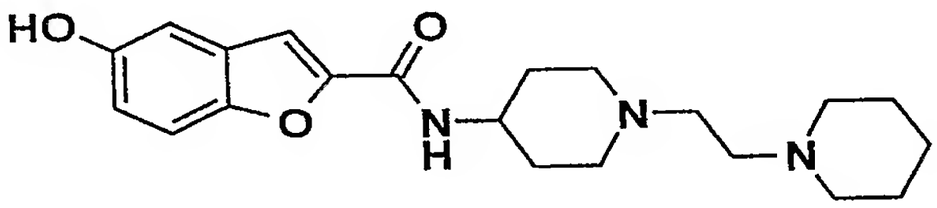
1. 5-Methoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized analogously to example 1 from 5-methoxy-benzofuran-2-carboxylic acid and amine **4**.
MS (ESI): 386.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 8.50 (d, NH), 7.55 (d, 1H), 7.47 (s, 1H), 7.27 (d, 1H), 7.06 (dd, 1H), 3.84 (s, 3H), 3.78 (m, 1H), 2.91 (m, 2H), 2.40 (m, 8H), 2.03 (m, 2H), 1.75 (m, 2H), 1.62 (m, 2H), 1.52 (m, 4H), 1.40 (m, 2H).

Example 97

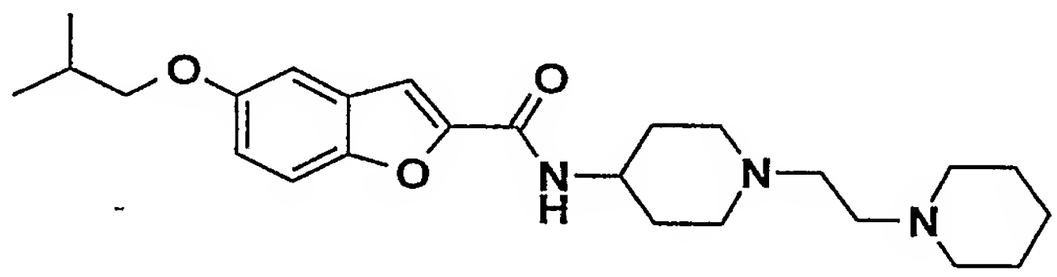
1. 5-Hydroxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized from the product of example **96** analogously to the method described in example **44**. MS (ESI): 372.3 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 9.38 (s, OH), 8.44 (s, NH), 7.46 (d, 1H), 7.39 (s, 1H), 7.03 (d, 1H), 6.92 (dd, 1H), 3.75 (m, 1H), 2.90 (m, 2H), 2.88 (m, 8H), 2.02 (m, 2H), 1.72 (m, 2H), 1.62 (m, 2H), 1.52-1.30 (m, 6H).

Example 98

1. 5-Isobutoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide



This compound is synthesized from the compound from Example 97 and isobutyl bromide analogously to the method described in Example **45**. MS (ESI): 428.4 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 8.50 (d, 1H), 7.55 (d, 1H), 7.45 (s, 1H), 7.28 (d, 1H), 7.06 (dd, 1H), 3.81 (d, 2H), 3.76 (m, 1H), 2.90 (m, 2H), 2.38 (m, 8H), 2.03 (m, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.50 (m, 4H), 1.40 (m, 2H), 1.02 (d, 6H).

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g.as CCR2 and CCR5 antagonists as indicated in in vitro tests as described below.

a) CCR2 membrane binding assay

The SPA (Scintillation Proximity Assay) technology is used to show that the test compounds prevent MCP-1 from binding to cell membranes expressing the CCR2 receptor. Transfected CHO-dukX cells stably expressing the hCCR2b gene are grown in MEM alpha medium to a confluency of between 70 and 80 %. After discarding the medium, 30 ml ice-cold physiological buffer solution containing 1 mM EDTA are added and the cells removed from the plate using a scraper. The cell suspension is centrifuged at 800 g for 10' at 4 °C and the cell pellet resuspended in buffer. Cell lysis is done using a Polytron PTI300D instrument at 28 000 RPM for 2 times 30 seconds on ice. Membranes are collected by centrifugation at 42 000 g for 20 minutes at 4 °C and subjected to a second round of lysis (Polytron, 28 000 RPM, 2x30 seconds on ice). Following centrifugation at 42 000 g for 20 minutes at 4 °C the membranes are resuspended in buffer at a protein concentration of 2 mg/ml and stored at -80 °C. Ten millimolar stock solutions of test compounds in 100% DMSO are prepared. Test compounds are further diluted in buffer to yield the four-fold concentrated solutions for the tests that assayed a range of 10^{-10} to 10^{-5} M. The SPA assay is performed in a final volume of 200 µl per well in 96 well plates. The components are added per well in the following order:

50 µl Buffer (+/- test compound)

50 µl Wheat germ agglutinin-SPA beads (1.25 mg/well) in buffer
50 µl CCR2B membrane suspension diluted with buffer to 0.04 mg/ml (2 µg/well), alternatively 50'000 cells per well
50 µl [^{125}I] MCP-1 in buffer (60 pM final concentration, 2.5 µCi/plate)

After addition of all components the plate is sealed and incubated for 90 minutes at room temperature with constant shaking. Following incubation the plate is centrifuged at 1000 RPM in a Sorvall RC3B centrifuge for 4 minutes at room temperature and counted for 3 minutes per well in a TOP COUNT instrument (Packard). The quench-corrected counts are used for the analysis of radioligand binding.
Compounds of formula I have an IC_{50} between 0.0003 and 10 µM.

In a similar manner, binding assays for the rat, mouse and rhesus monkey CCR2 receptors have been established. Due to the species specificity of the CCR2 antagonists, the compounds of formula I have an IC_{50} between 0.015 and 10 µM on mouse CCR2 and between 0.020 and 10 µM on rat CCR2.

b) CCR2 functional assay – Ca2+ mobilization

hCCR2b-CHO#84 cells:

CHOdukX cell line stably expressing the hCCR2 gene is grown in MEMα up to a confluence of 80%. The day before the experiment, cells are harvested from the tissue culture flask by trypsinization, washed, plated in a black/clear bottom 96-well plate at $5x10^4$ cells per well and cultured overnight at 37°C in a humid atmosphere enriched with 5% CO_2. On the next day, cells are washed twice and loaded for 1 hour at RT in the dark with 2 µM Fluo-4 in buffer C. After two further washes, the cells are resuspended in buffer D. Serial dilutions of the compounds, in buffer D, are mixed with the cells and incubated for half an hour at RT in the dark. Cells are then stimulated by the injection of MCP-1 and calcium fluxes are monitored using the Flexstation™, a benchtop scanning fluorometer with and integrated fluid transfer workstation.

	HBSS* 1X	20mM Hepes	0.1% BSA	625µM Probenecid	0.5% BSA
Buffer A	X	X			
Buffer B	X	X	X		
Buffer C	X	X		X	
Buffer D	X	X		X	X

* Hank's balanced alt Solution (10X) without phenol red (#14065-049, Gibco BRL).

hCCR2b-300.19 cells:

Pre-B cell line 300-19 stably expressing the hCCR2 gene (Loetscher et al., J. Biol. Chem. 276 (5), 2986-91 (2001)) is grown in RPMI 1640 with glutamax-I supplemented with 1X MEM non essential amino-acid, 1 mM sodium pyruvate, $5x10^{-5}$ M β-mercaptoethanol and 10 % FCS. For the experiment, the cells are used in the exponential growing phase, at a maximal concentration of $1.5x10^6$ cells per ml. Cells are washed in buffer A and loaded at about 2.10^6 cells per ml in 2 µM fluo-4 in buffer B for 30 min. in the dark, at 37°C in a waterbath. After two washes with buffer A, cells are plated in black/clear bottom 96-well plate at $2x10^5$ cells per well in buffer B. All following steps, including the compound and the chemokine dilutions, are performed as described above for the hCCR2b-CHO#84 cells, except that buffer B is used instead of buffer D.

In this assay, compounds of formula I have an IC_{50} between 0.0005 and 10 µM.

c) CCR2 functional assay – chemotaxis

An *in vitro* cell migration assay for CCR2-dependent chemotaxis based on Transwell™ membrane inserts is used to profile the compounds. The assay is performed with the human monocytic THP-1 cell line and activated peripheral blood lymphocytes (PBL). THP-1 cells are cultured in RPMI1640 supplemented with 10 % heat-inactivated FCS. Activated PBL are prepared from human blood by elutriation and then activated by culture on anti-human CD3-coated culture plates and expanded by subsequent culture in medium supplemented with IL-2. Aliquots of activated PBL are frozen in liquid nitrogen and used in migration experiments after thawing and overnight culture. Cells from cultures at a density of less than 1.2 x 106 cells/ml are counted, washed and resuspended at an appropriate density in RPMI1640 containing 0.5 % BSA. Transwell™ membrane inserts of 6.5 mm diameter, 3 or 8 µm pore size and tissue culture treated polycarbonate membrane are used for the migration assays. The transwell inserts are loaded with cells and compounds in a final volume of 100 µl in RPMI1640/0.5 % BSA. For THP-1 cells, 8 µm pore size inserts are used. For PBLs the use of 3 µm pore size inserts resulted in lower non-specific counts. The inserts are placed in a 24-well tissue culture plate containing recombinant human MCP-1 and compounds in a final volume of 600 µl. After allowing the cells to migrate to the bottom compartment, the assay is stopped by removing and discarding the transwell inserts. Cells in the bottom compartment are collected and counted on a FACScan flow cytometer by acquiring all events for 30 s with

settings established for each cell type. Migration is expressed as absolute cell counts/30 s relative to the input cell number measured under the same conditions.

In this assay, compounds of formula I have an IC_{50} between 0.0012 and 10 μM.

d) CCR5 membrane binding assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. Membranes prepared from these CCR5 transfectants are used in a radioligand binding assay using 125-I-MIP-1α as a ligand and the compounds of formula I are tested for inhibitory activity. The data are reported as IC_{50}, i.e. the concentration of compound required to achieve 50% inhibition of [I-125]MIP-1α binding. In this assay, compounds of formula I have an IC_{50} between 0.004 and 10 μM.

Agents of the invention are useful for the prophylaxis and treatment of CCR-2 and CCR-5 mediated diseases or medical conditions. CCR-2 and CCR-5 play an important role in leukocyte trafficking, in particular in monocyte migration to inflammatory sites and thus the agents of the invention may be used to inhibit monocyte migration e.g. in the treatment of inflammatory conditions, allergies and allergic conditions, autoimmune diseases, chronic pain, graft rejection, cancers which involve leukocyte filtration, stenosis or restenosis, atherosclerosis, rheumatoid arthritis, osteoarthritis and chronic pain.

Diseases or conditions which may be treated with the Agents of the Invention include:

Inflammatory or allergic conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, COPD, hypersensitivity lung diseases, hypersensitivity pneumonitis, interstitial lung disease (ILD), (e.g. idiopathic pulmonary fibrosis, or ILD associated with autoimmune diseases such as RA, SLE, etc.); anaphylaxis or hypersensitivity responses, drug allergies (e.g. to penicillins or cephalosporins), and insect sting allergies; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies, sclerodoma; psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis;

Autoimmune diseases, in particular autoimmune diseases with an aetiology including an inflammatory component such as arthritis (for example rheumatoid arthritis, arthritis chronica

progrediente, psoriatic arthritis and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific auto-immune diseases for which Antibodies of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma; Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), autoimmune thyroiditis, Behcet's disease, endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy);
graft rejection (e.g. in transplantation including heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, or corneal transplants) including allograft rejection or xenograft rejection or graft-versus-host disease, and organ transplant associated arteriosclerosis;
atherosclerosis;
cancer with leukocyte infiltration of the skin or organs;
stenosis or restenosis of the vasculature, particularly of the arteries, e.g. the coronary artery, including stenosis or restenosis which results from vascular intervention, as well as neointimal hyperplasia;
and other diseases or conditions involving inflammatory responses including reperfusion injury, hematologic malignancies, cytokine induced toxicity (e.g. septic shock or endotoxic shock), polymyositis, dermatomyositis, and granulomatous diseases including sarcoidosis.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy e.g. in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or preclinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of premalignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g.

squamus or basal cell carcinoma consequential to UV light exposure, e.g. resultant from chronic exposure to the sun.

Agents of the Invention are particularly useful for treating diseases of bone and cartilage metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides, e.g. rheumatoid arthritis, and bone loss in general, including age-related bone loss, and in particular periodontal disease.

The Agents of the Invention may also be used in ocular applications which include the treatment of ocular disorders, in particular of ocular inflammatory disorders, of ocular pain including pain associated with ocular surgery such as PRK or cataract surgery, of ocular allergy, of photophobia of various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response (TIGR) protein, and of dry eye disease.

For the above indications, the appropriate dosage will, of course, vary depending upon, for example, the particular Agent of the Invention to be employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in prophylactic use, satisfactory results are generally indicated to be obtained at dosages from about 0.05 mg to about 10 mg per kilogram body weight, more usually from about 0.1 mg to about 5 mg per kilogram body weight. The frequency of dosing for prophylactic use will normally be in the range from about once per week up to about once every 3 months, more usually in the range from about once every 2 weeks up to about once every 10 weeks, e.g. once every 4 or 8 weeks. Agent of the Invention is conveniently administered parenterally, intravenously, e.g. into the antecubital or other peripheral vein, intramuscularly, or subcutaneously. For example, a prophylactic treatment typically comprises administering the Antibody of the Invention once per month to once every 2 to 3 months, or less frequently.

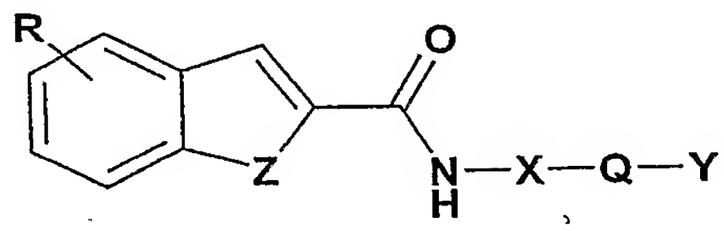
Pharmaceutical compositions of the invention may be manufactured in conventional manner. A composition according to the invention is preferably provided in lyophilized form. For immediate administration it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline. If it is considered desirable to make up a solution of larger volume for administration by infusion rather as a bolus injection, it is advantageous to incorporate human serum albumin or the patient's own heparinised

blood into the saline at the time of formulation. The presence of an excess of such physiologically inert protein prevents loss of antibody by adsorption onto the walls of the container and tubing used with the infusion solution. If albumin is used, a suitable concentration is from 0.5 to 4.5% by weight of the saline solution.

The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg of Agent of the Invention per unit dosage.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof:



(I)

Wherein:

Z is CR_1R_2, NR_3, O or S;

R represents one or more ring substituents selected from the group consisting of H, hydroxy, an optionally substituted lower alkoxy, lower alkenyloxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl-lower alkoxy or heteroaryl-lower alkoxy, an optionally substituted lower alkyl or lower alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group;

R_1, R_2, and R_3 are independently selected from the group consisting of H and lower alkyl;

X is a C_3-C_{18} cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which may be optionally substituted;

Q is a linker of between 1 and 3 atoms in length;

Y is C_3-C_{18} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocyloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

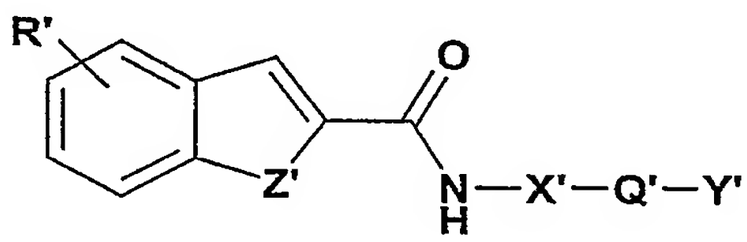
the optional substituent or substituents on R being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18}

heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on X being independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on Y being independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

2. A compound of formula (II), or a pharmaceutically acceptable salt, ester or prodrug thereof:



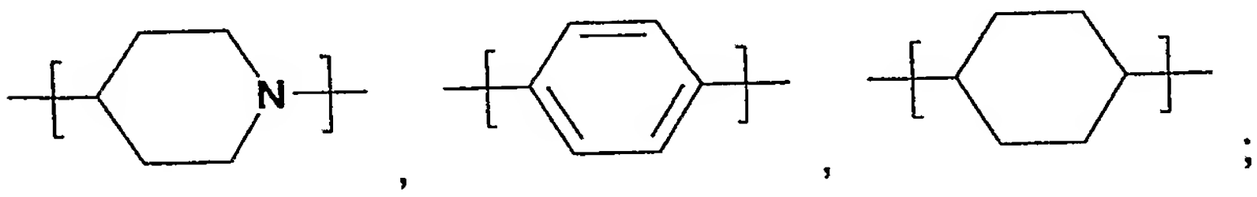
(II)

wherein:

Z' is NH, NCH_3, CH_2, S or O;

R' is hydroxy, an optionally substituted lower alkoxy, alkenyloxy, cycloalkyl-lower alkyloxy, aryloxy, heteroaryloxy, heteroaryl-lower alkyloxy or aryl-lower alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group;

X' is selected from the group consisting of:



;

Q' is selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y' is selected from the group consisting of: optionally substituted piperidinyl, azepanyl, azocanyl, phenyl, tetrahydropyranyl, 8-aza-bicyclo[3.2.1]oct-8-yl, tetrahydropyridinyl, octahydro-quinolizinyl, each of which is optionally substituted;

the optional substituent or substituents on R' being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on X' being independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on Y' being independently selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

3. A compound according to any one of the preceding claims selected from:

5-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Benzyloxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

6-Methoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

4,6-Dimethoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide-dihydrochloride

5,6-Dimethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

6-Benzyloxy-5-methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-cyclohexyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide

5-Hydroxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

6-Hydroxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

5-(2-Methyl-allyloxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

6-Isobutoxy-1H-indole-2-carboxylic acid[1-(2-azepan-1-yl-ethyl)piperidin-4-yl]-amide

6-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid[1-(2-azepann-1-yl-ethyl)piperidin-4-yl]-amide

4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide ;

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2R-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2S-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1R-methyl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1S-methyl-ethyl)-piperidin-4-yl]-amide

7-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

5-Methoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

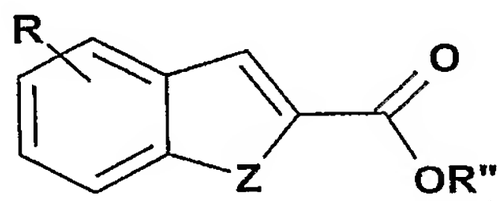
5-Hydroxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide

5-Isobutoxy-benzofuran-2-carboxylic acid[1-(2-piperidin-1-yl-ethyl)piperidin-4-yl]-amide.

4. A compound according to any one of the preceding claims for use as a pharmaceutical for the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

5. A process for the preparation of a compound of formula (I) comprising:

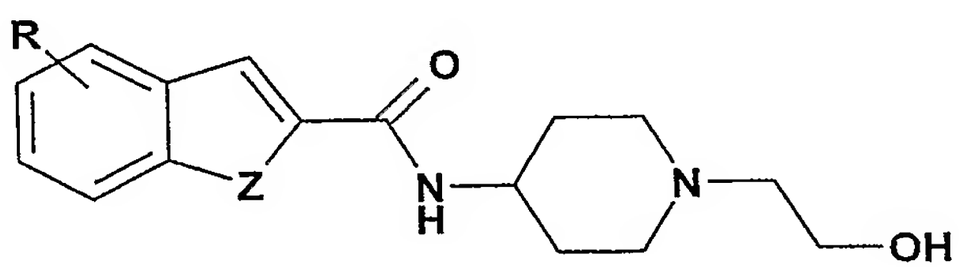
(a) reacting a compound of formula (III):



(III)

wherein R" is H or a lower alkyl group, with a compound of formula NH_2-X-Q-Y, the groups R, Z, X, Q and Y being defined in claim 1; or

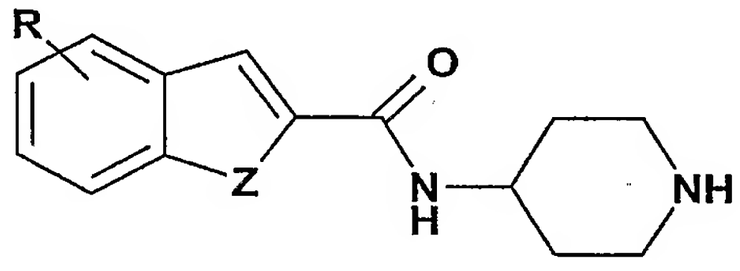
(b) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is $-CH_2-CH_2-$, and Y is a group having the formula $-NR_7R_8$ wherein N, R_7 and R_8 are linked to define collectively a heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, heteroaryl, or fused aryl-heterocycloalkyl, reacting a compound of formula (IV):



(IV)

with a compound of formula NHR_7R_8, wherein R_7 and R_8 are as defined above, and R and Z are as defined in claim 1; or

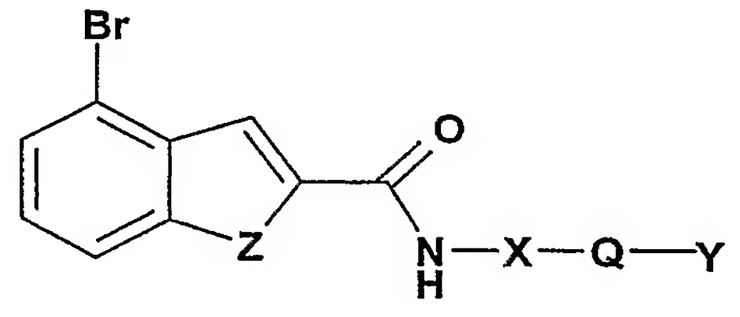
(c) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is CH_2-, reacting a compound of formula (V):



(V)

in which R and Z are as defined in claim 1, with a compound of formula HO-CH_2-Y, in which Y is as defined in claim 1; or

(d) for the preparation of compounds of formula (I) wherein R represents one or more ring substituents as defined in claim 1 and wherein one of said substituents is an optionally substituted aryl group and is located at the 4 position of the ring, appropriately substituting the Br group in a compound of formula (VI) for said substituted aryl group:



(VI)

wherein Z, X, Q and Y are as defined in claim 1;

and recovering the resultant compounds of formula (I) in free or salt form.

6. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier.

7. Use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of an autoimmune or inflammatory disease or condition.

8. A method of inhibiting chemokine receptors or macrophage protein or of reducing inflammation in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound according to claim 1.

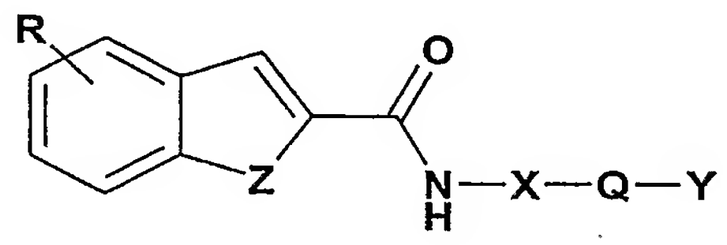
9. A method of treating an inflammatory or autimmune disease or condition, comprising administering to said subject an effective amount of a compound according to claim 1.

9. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples.

ABSTRACT

Organic compounds

A compound of formula (I) or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

wherein the variants R, Z, X, Q and Y are defined in the specification.